ALKS 3831: A Novel Drug Candidate for the Treatment of Schizophrenia

Investor Presentation

MAY 10, 2018

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Agenda

- Introduction to ALKS 3831
- ALKS 3831 Mechanism: Preclinical Observations of Olanzapine and Samidorphan
  - Central and Whole Body Effects
  - Acute and Long-Term Effects
- Translational Phase 1 Metabolic Results
- Clinical Results Overview
  - Phase 2 Weight and Efficacy Data
  - Phase 3 Development Program
- Conclusions and Next Steps

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Introduction to ALKS 3831 for Schizophrenia

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ALKS 3831 for Schizophrenia

- Investigational, novel, once-daily, oral atypical antipsychotic drug candidate designed to offer robust efficacy with a favorable weight and metabolic profile
  - Administered once daily as a single, bi-layer tablet
- Differentiated mechanism of action
  - Fixed dose combination of olanzapine and a novel opioid antagonist samidorphan
    - Samidorphan included to potentially attenuate adverse metabolic sequelae of olanzapine
  - Central and peripheral effects on metabolism and weight gain in both acute and chronic settings
- Nearing completion of pivotal program
  - Beneficial weight effects demonstrated in phase 2 study
  - Antipsychotic efficacy proven in phase 3 study
  - Topline results from pivotal six-month weight study expected Q4’18
  - NDA submission planned H1 2019

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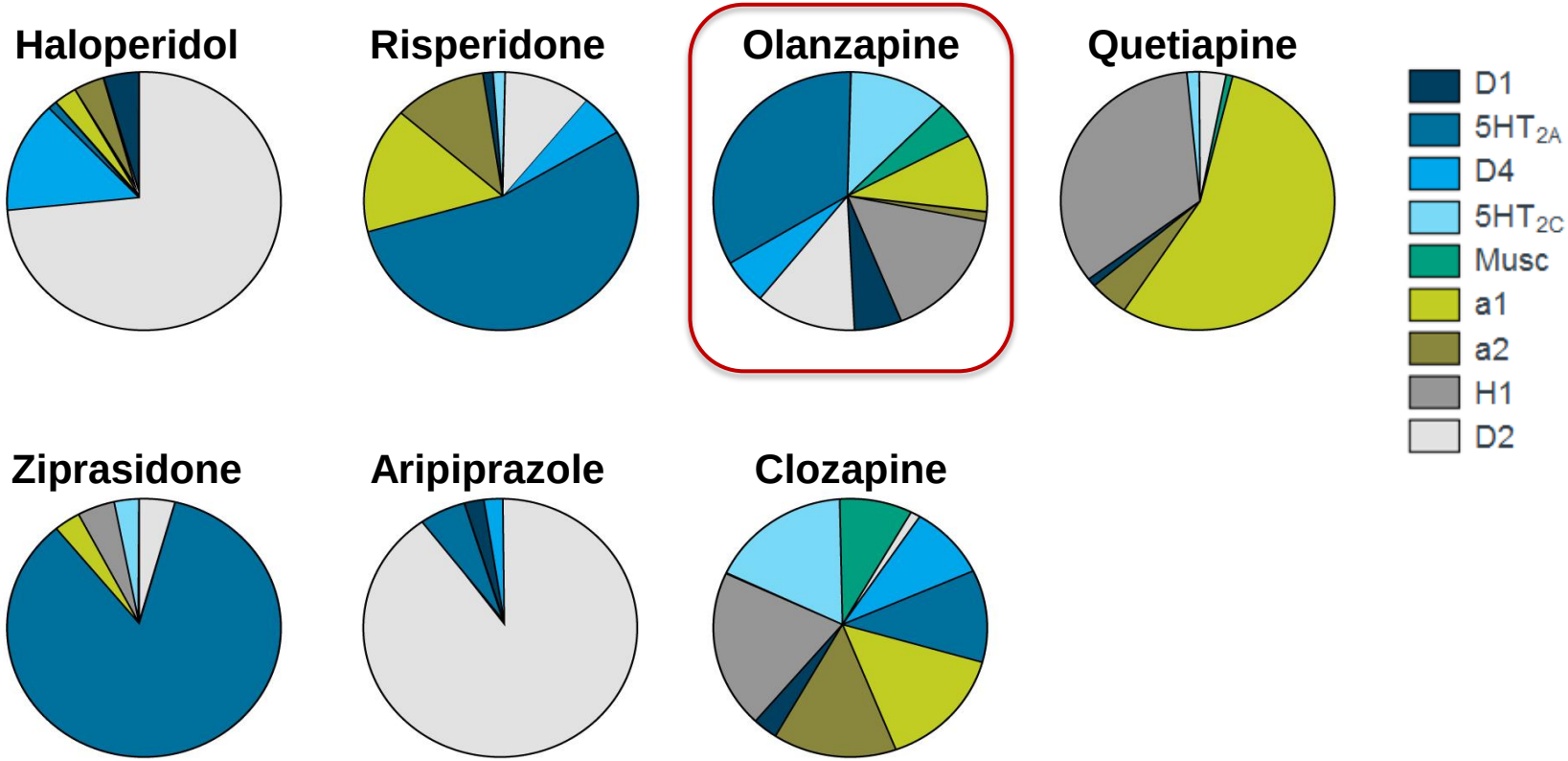
Receptor Binding Activity of Antipsychotics: Drivers of Efficacy and Side Effects Difficult to Separate



Sources: Bymaster FP, et al. *Neuropsychopharmacology.* 1996,14(2):87-96.
Schotte A, et al. *Psychopharmacology* (Berl). 1996, 124(1-2):57-73.

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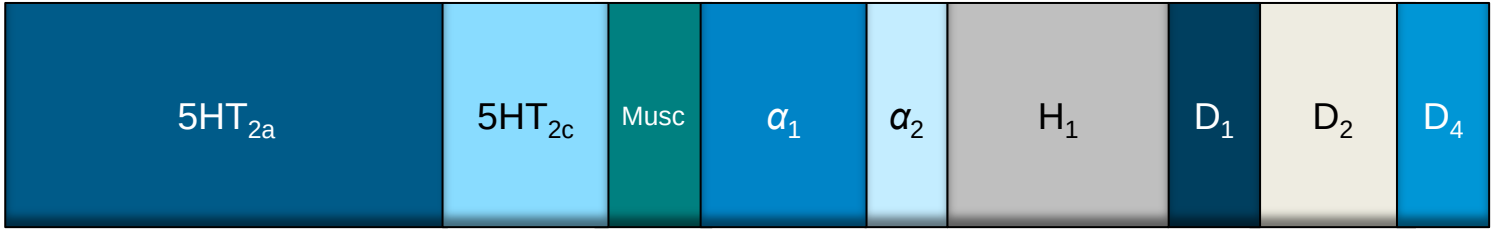
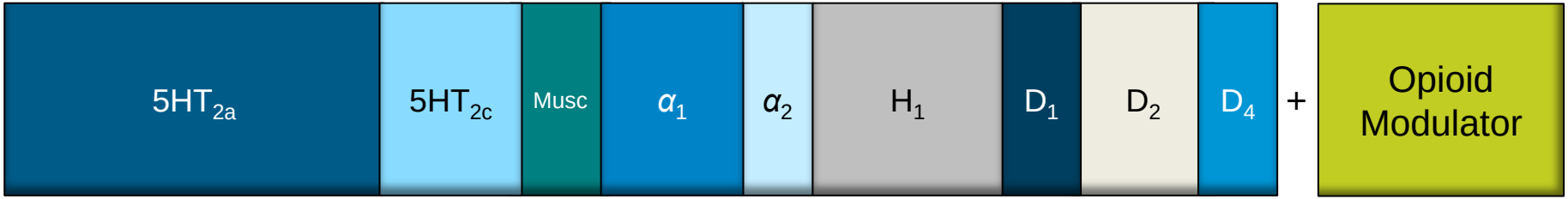
ALKS 3831 Design Rationale: Retain Olanzapine's Pharmacology Driving Efficacy and Address Metabolic Issues Through a Different System

Olanzapine Pharmacology



ALKS 3831 Pharmacology



Source: Bymaster FP, et al. *Neuropsychopharmacology.* 1996,14(2):87-96

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ALKS 3831 Mechanism: Preclinical Models Recapitulate Olanzapine-Driven Weight Gain

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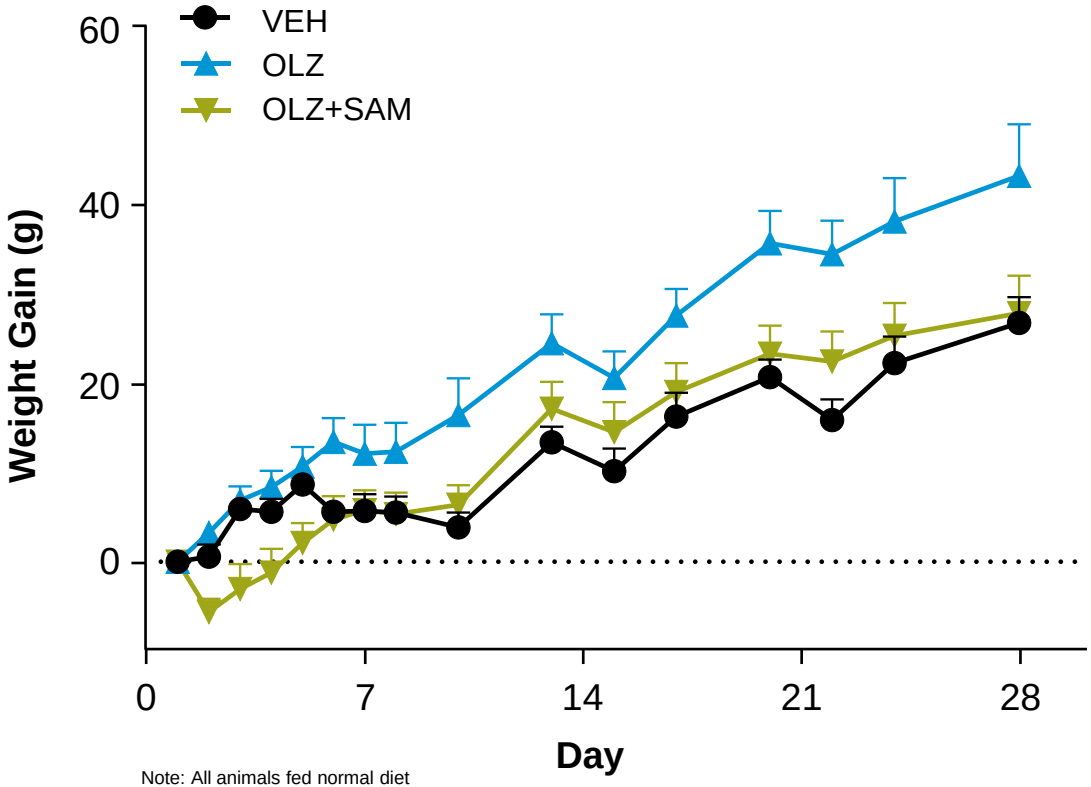
Samidorphan Attenuates Olanzapine-Induced Weight Gain in Female Rats



Note: All animals fed normal diet

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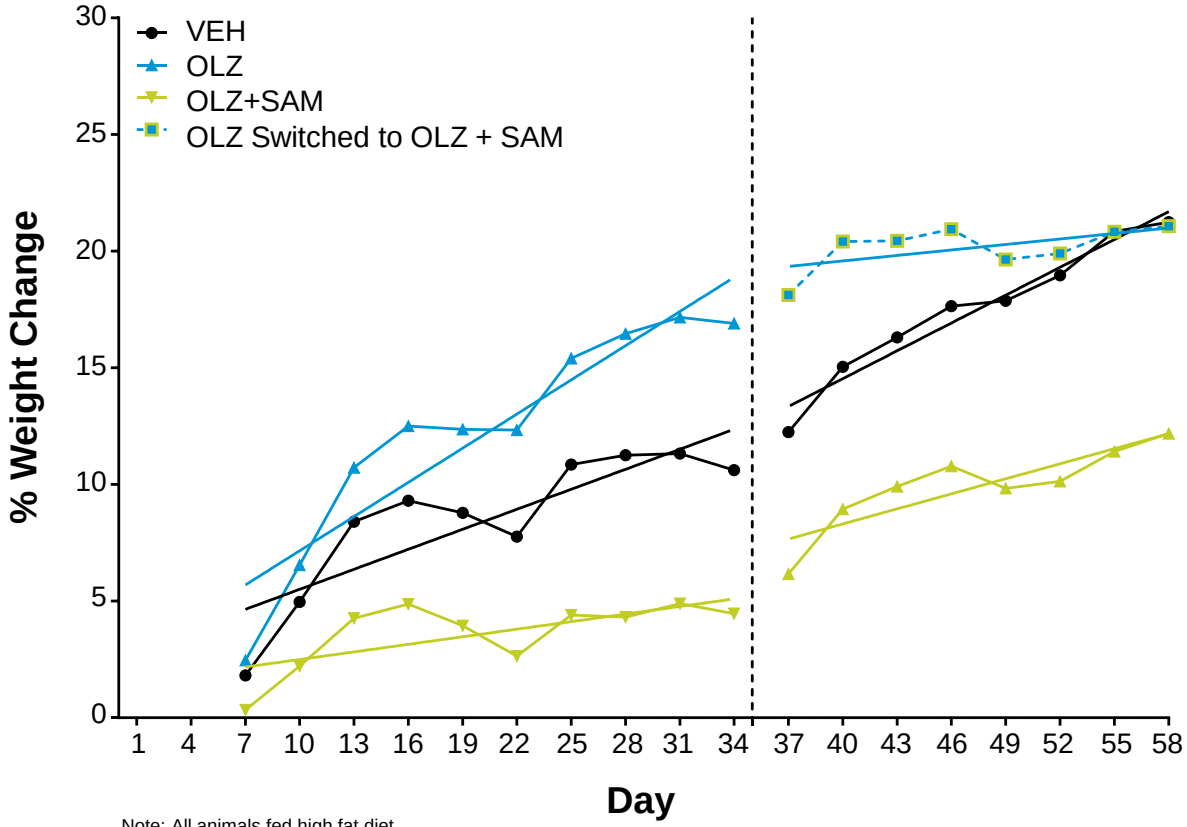
Samidorphan Attenuates Olanzapine-Induced Weight Gain in Female Non-Human Primates (NHPs)



Note: All animals fed high fat diet
Individual data points in graph represent rolling average of previous three data points

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ALKS 3831 Development Pathway

SAM Affects OLZ-Induced Weight Gain in Animals

Registration

Phase 1 POC Volunteers

Phase 2
Efficacy + Weight
N=309 Patients

Phase 3

ENLIGHTEN-1
Efficacy
N=403 Patients

ENLIGHTEN-2
Weight
N=~540 Patients

NDA for Schizophrenia

Mechanism

Preclinical

What?
Weight / Adiposity

How?
Brain: Food Reward
Periphery: Metabolism

Clinical

Acute
Translational Metabolism Study in Volunteers

Chronic
Future Studies in Patients

Mechanistic Understanding and Data

ALKS 3831:
Positioned for Expanded Use in Psychiatry

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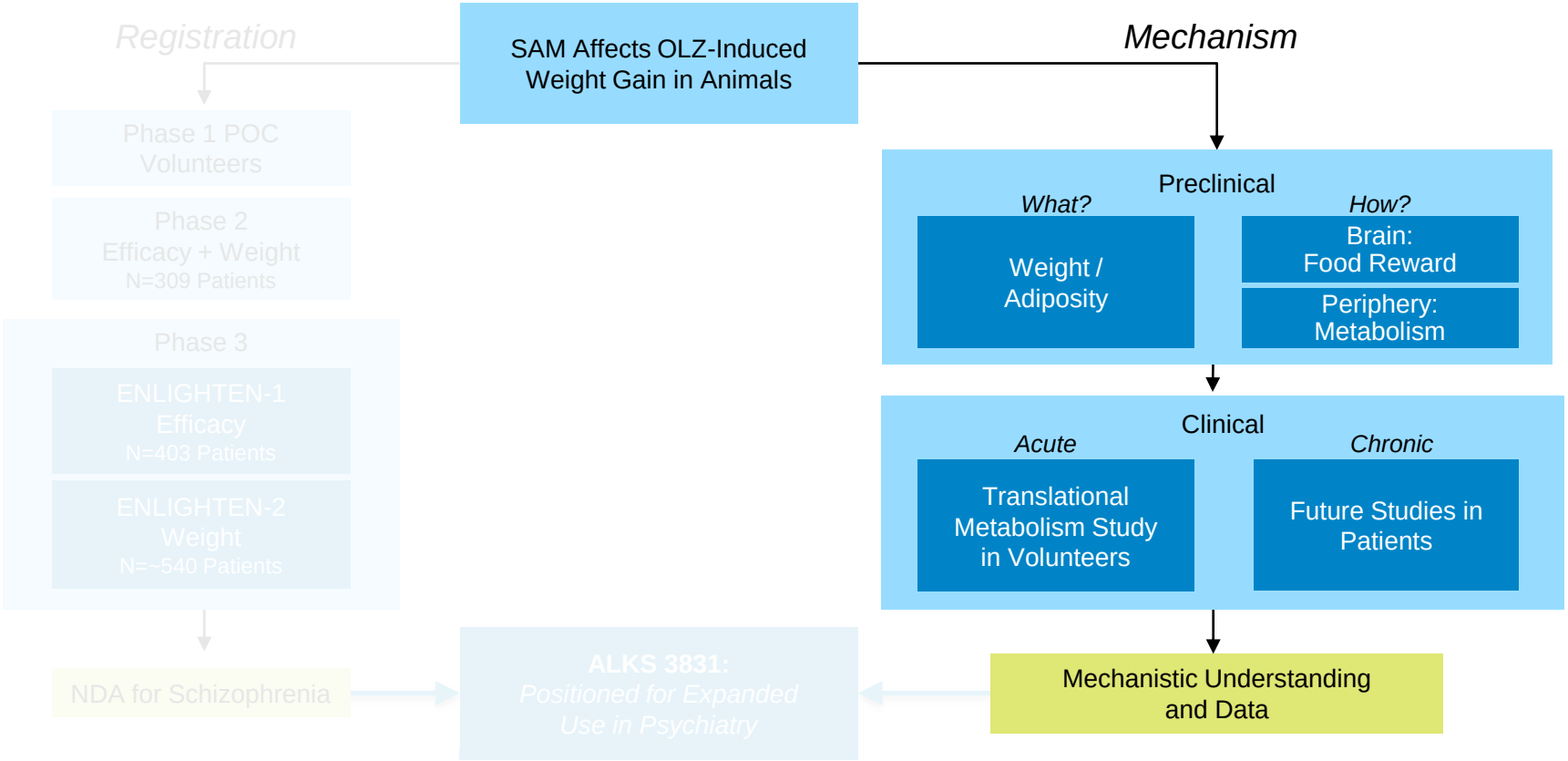

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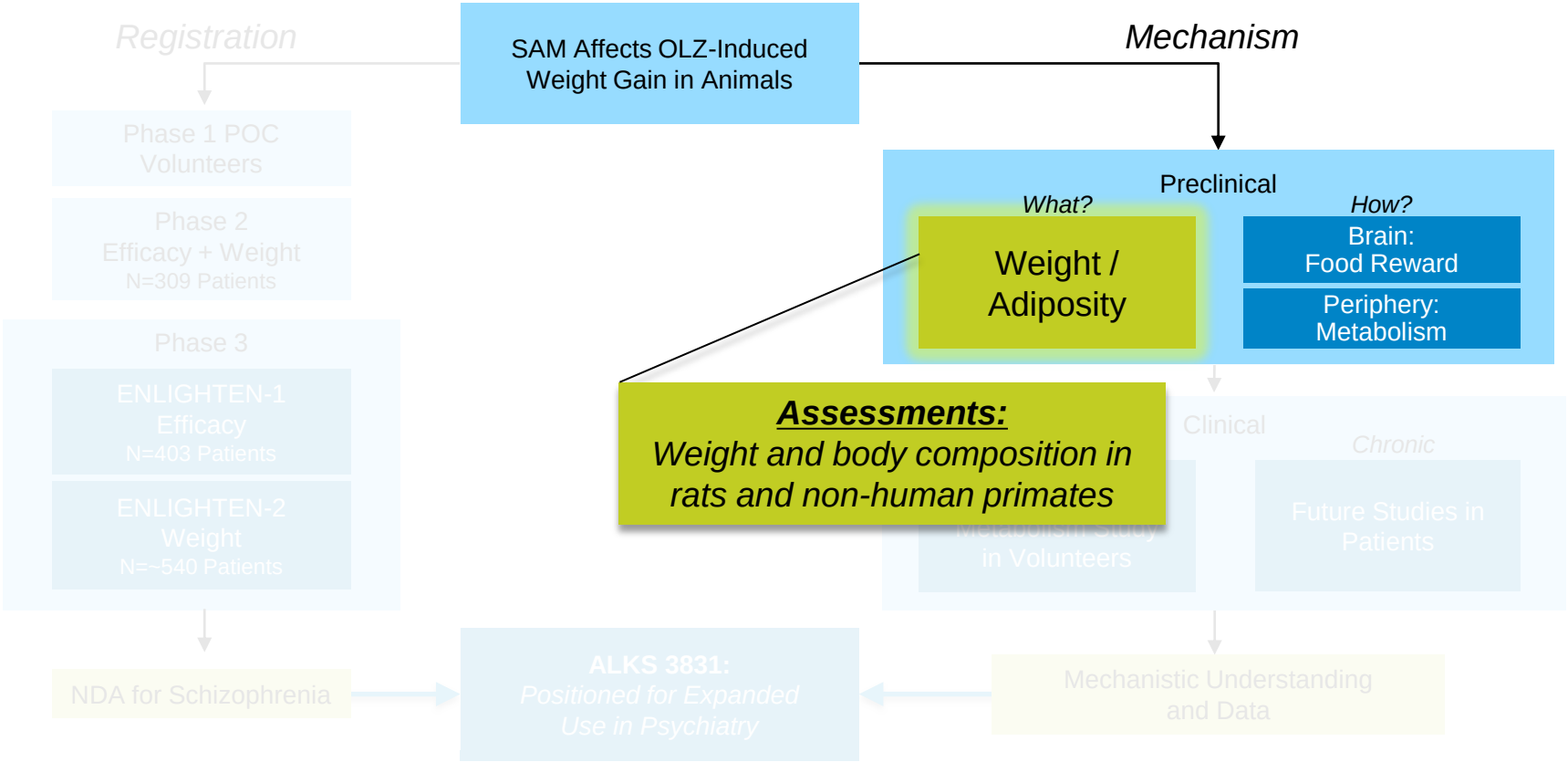

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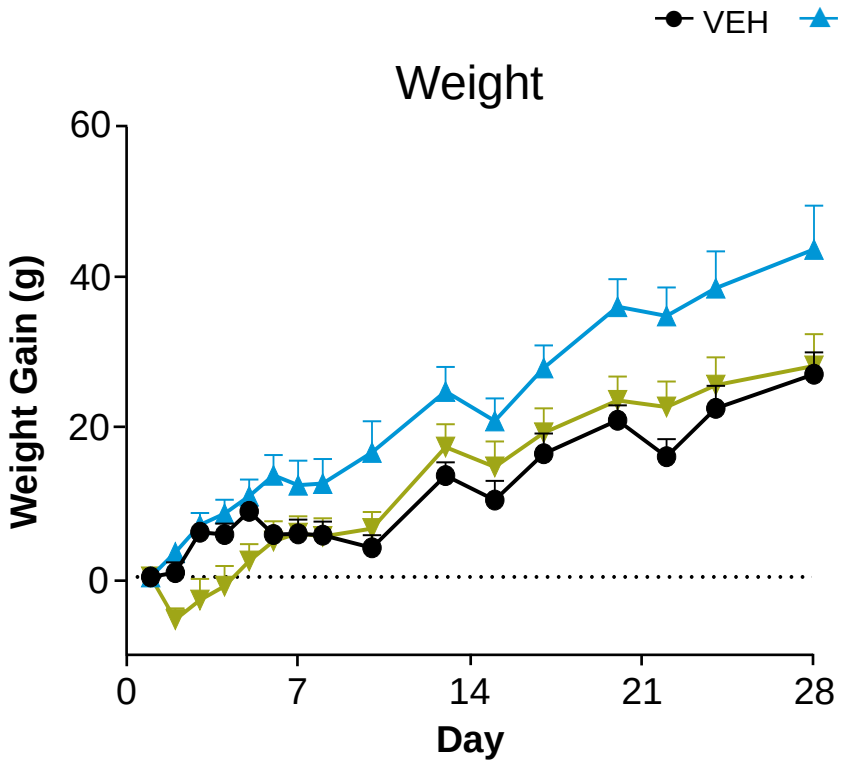
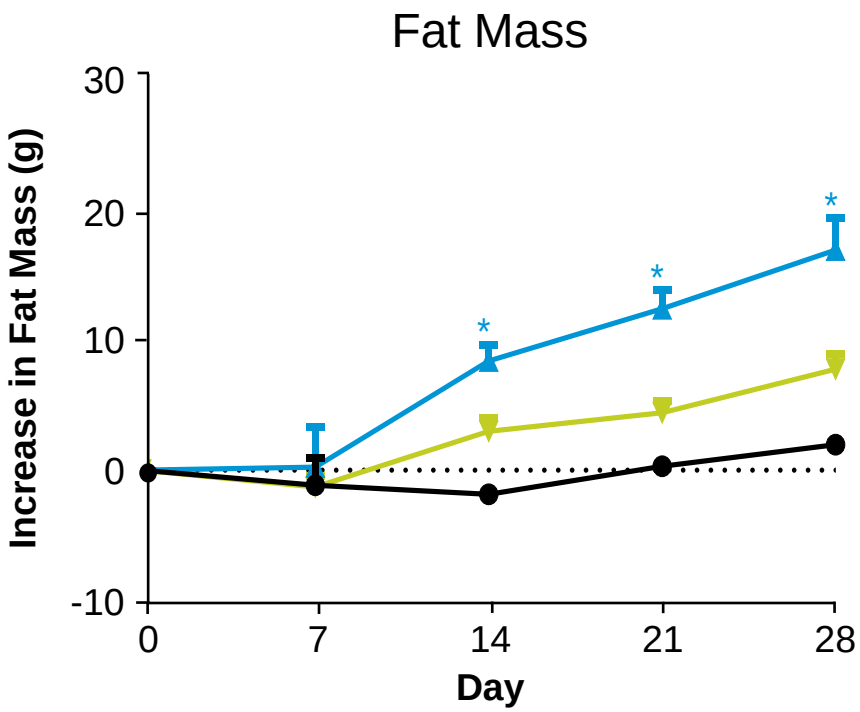
Samidorphan Attenuates Both Olanzapine-Induced Weight Gain and Increased Adiposity in Female Rats





Note: All animals fed normal diet

*OLZ vs. VEH, p<0.05

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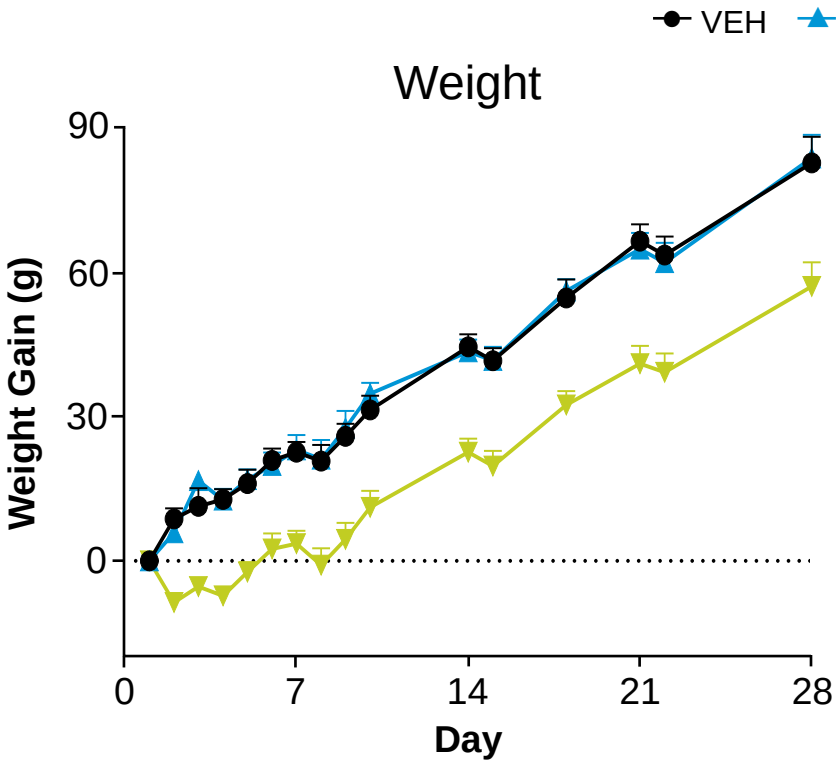
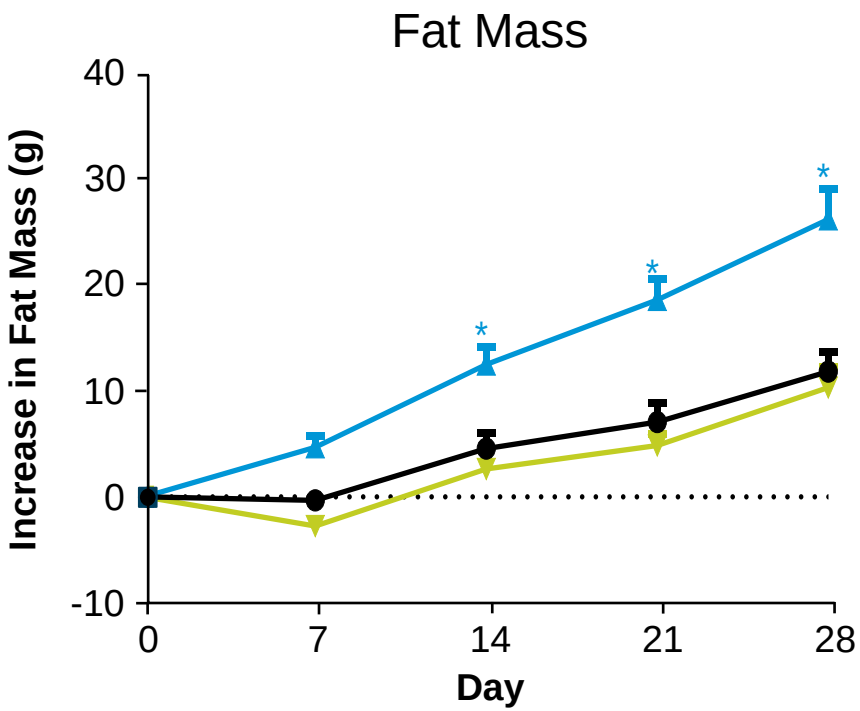
Samidorphan Attenuates Olanzapine-Induced Adiposity in Male Rats





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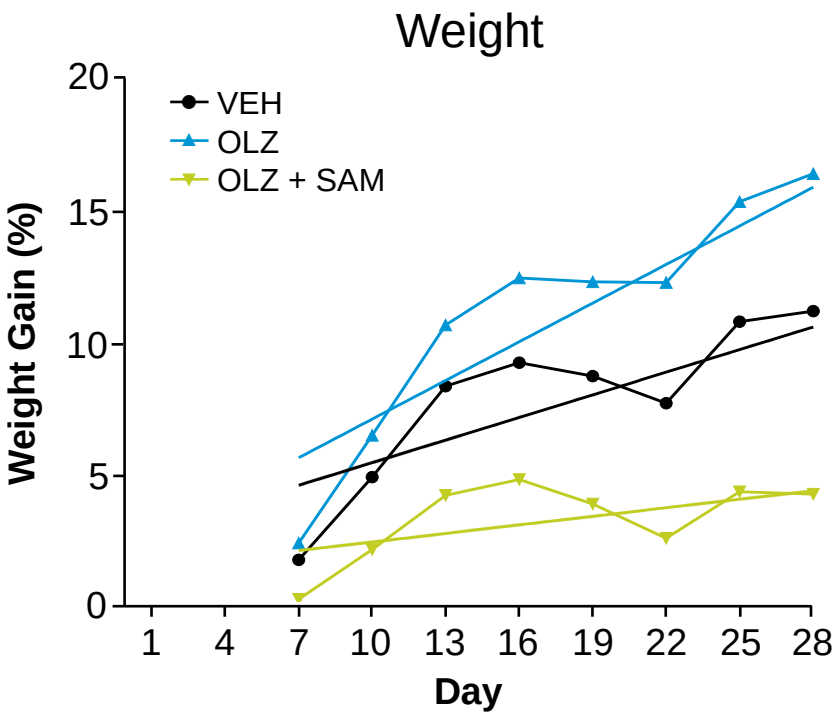
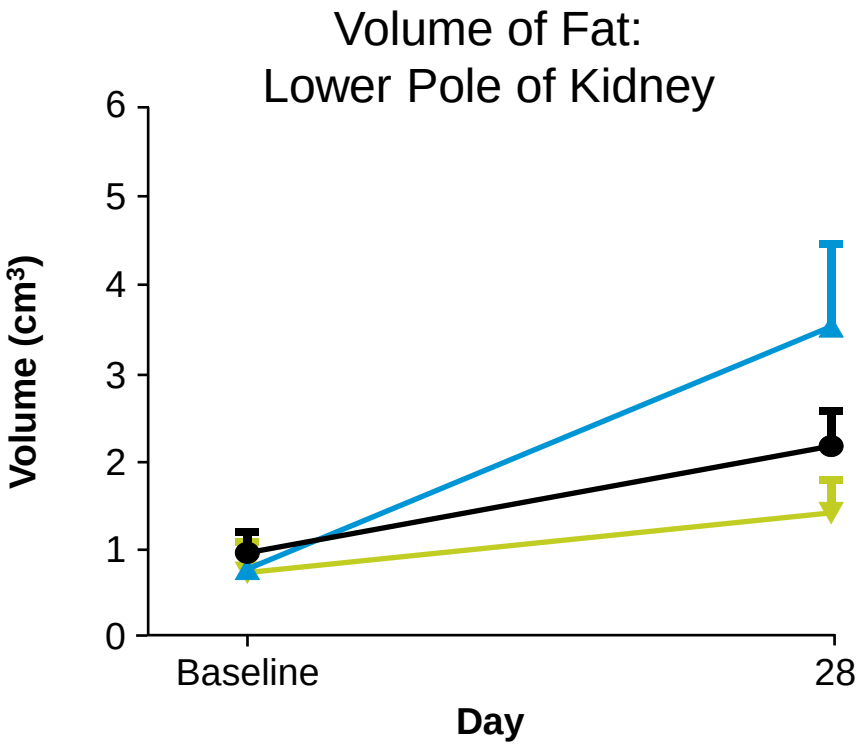
Samidorphan Decreases Adiposity Accretion in Female NHPs





Note: All animals fed high fat diet
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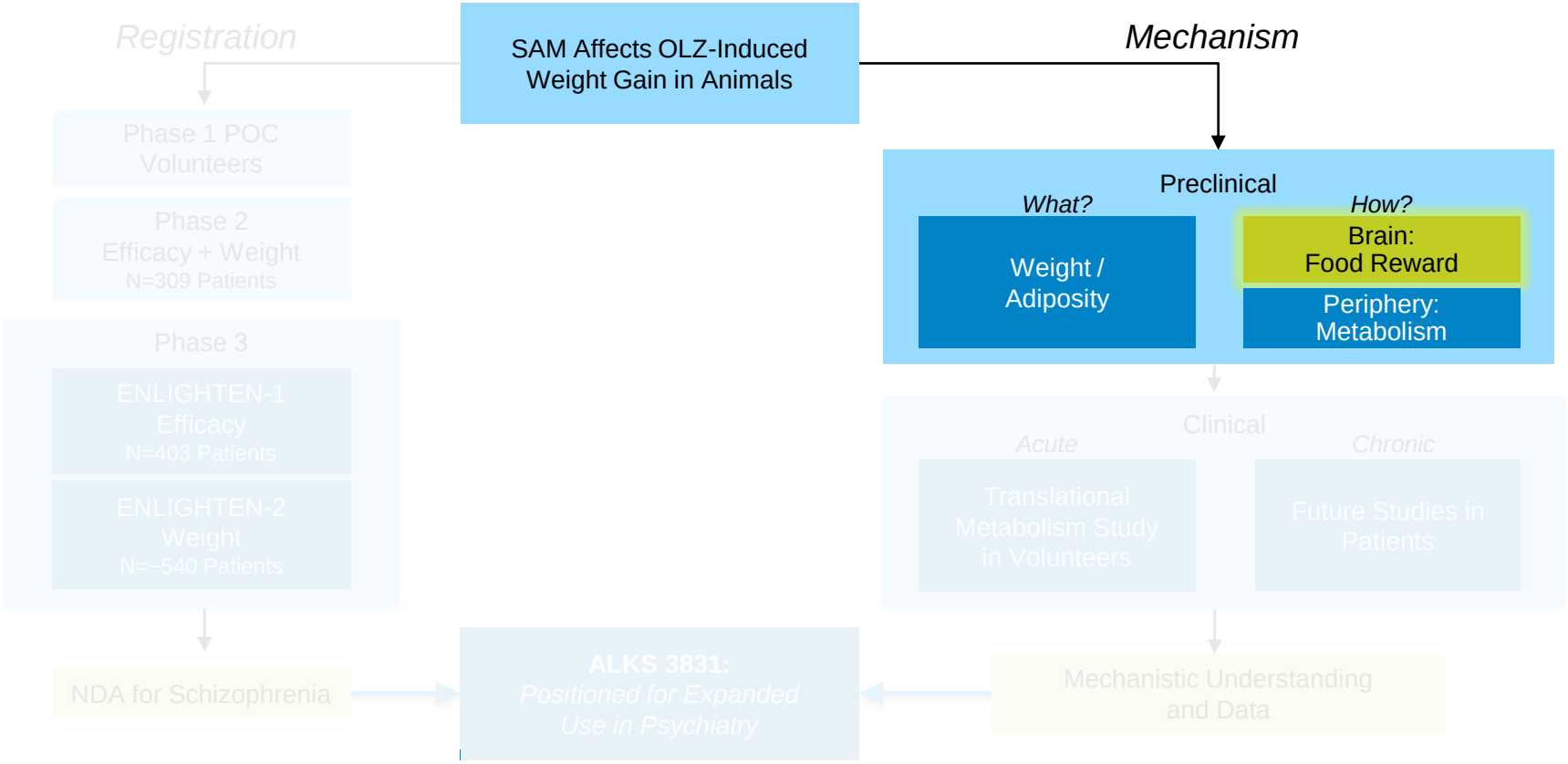

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Food Consumption Activates Reward Pathway in the Brain: Olanzapine Amplifies Normal Food Reward Pathway

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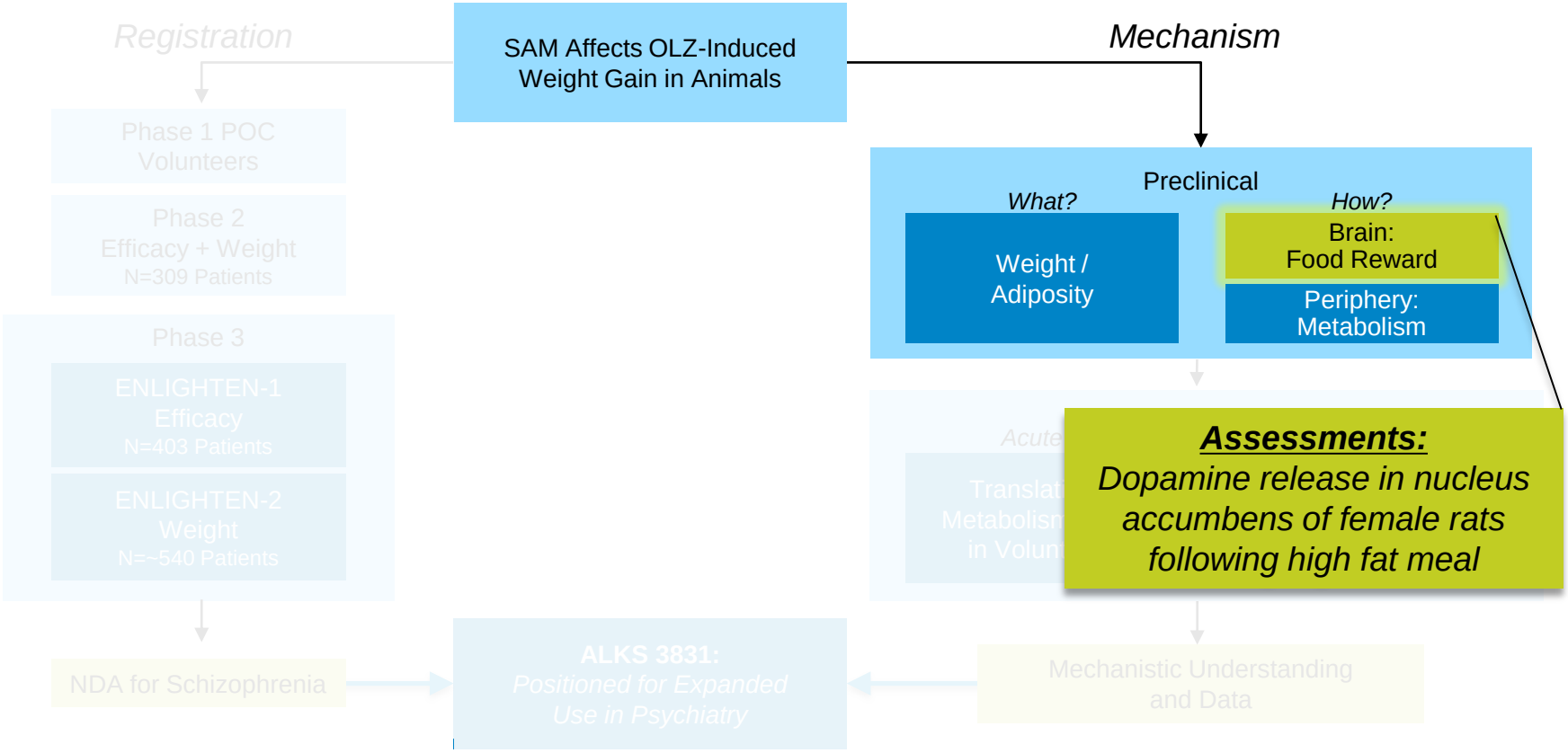
ALKS 3831 Development Pathway



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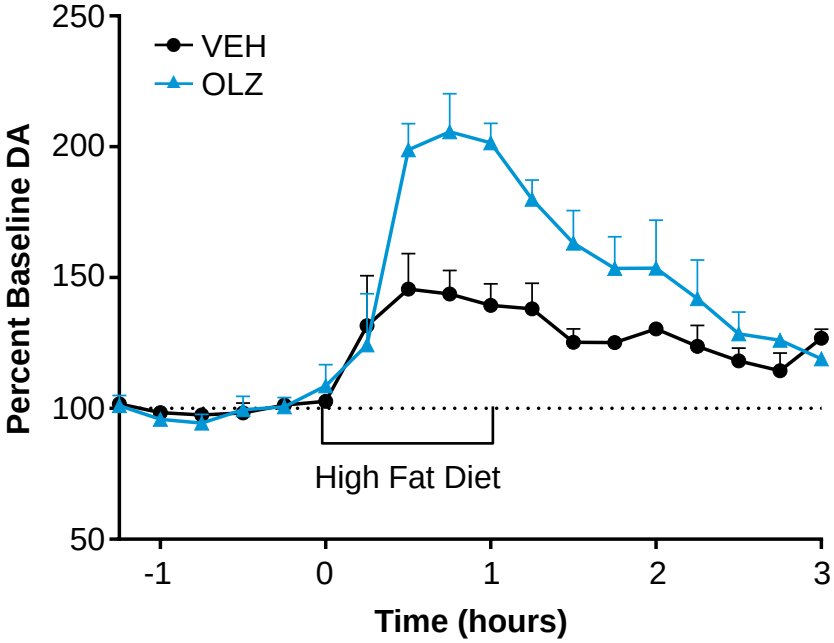
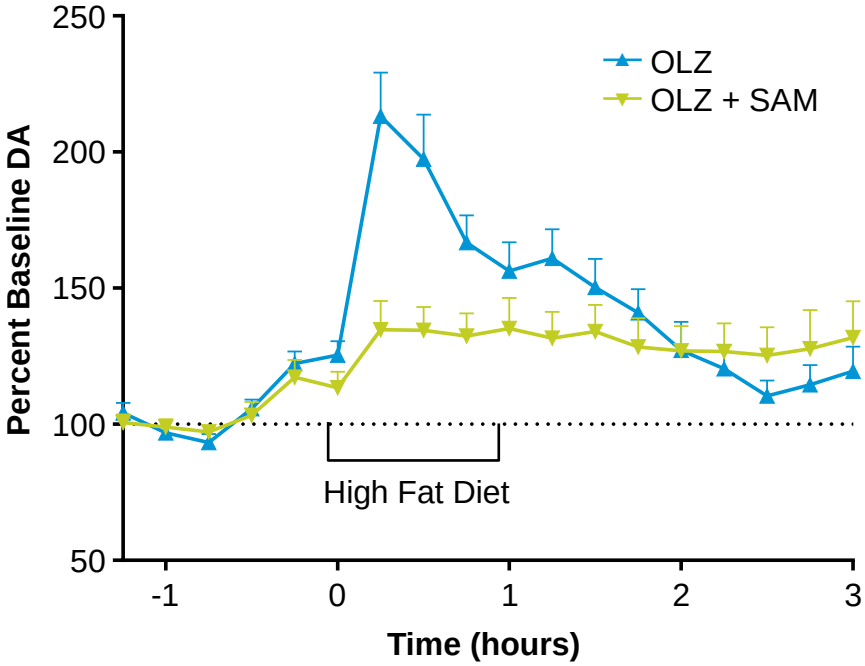
Samidorphan Attenuates Olanzapine-Induced Increase in Dopamine Response to High Fat Diet in Reward Pathway in Rats



*OLZ vs. VEH, $p < 0.05$



*OLZ vs. OLZ + SAM, $p < 0.01$

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ALKS 3831 Development Pathway

SAM Affects OLZ-Induced Weight Gain in Animals

Mechanism

Preclinical

What?

Weight / Adiposity

How?

Brain: Food Reward

Periphery: Metabolism

Clinical

Acute

Translational Metabolism Study in Volunteers

Chronic

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Mechanistic Understanding and Data

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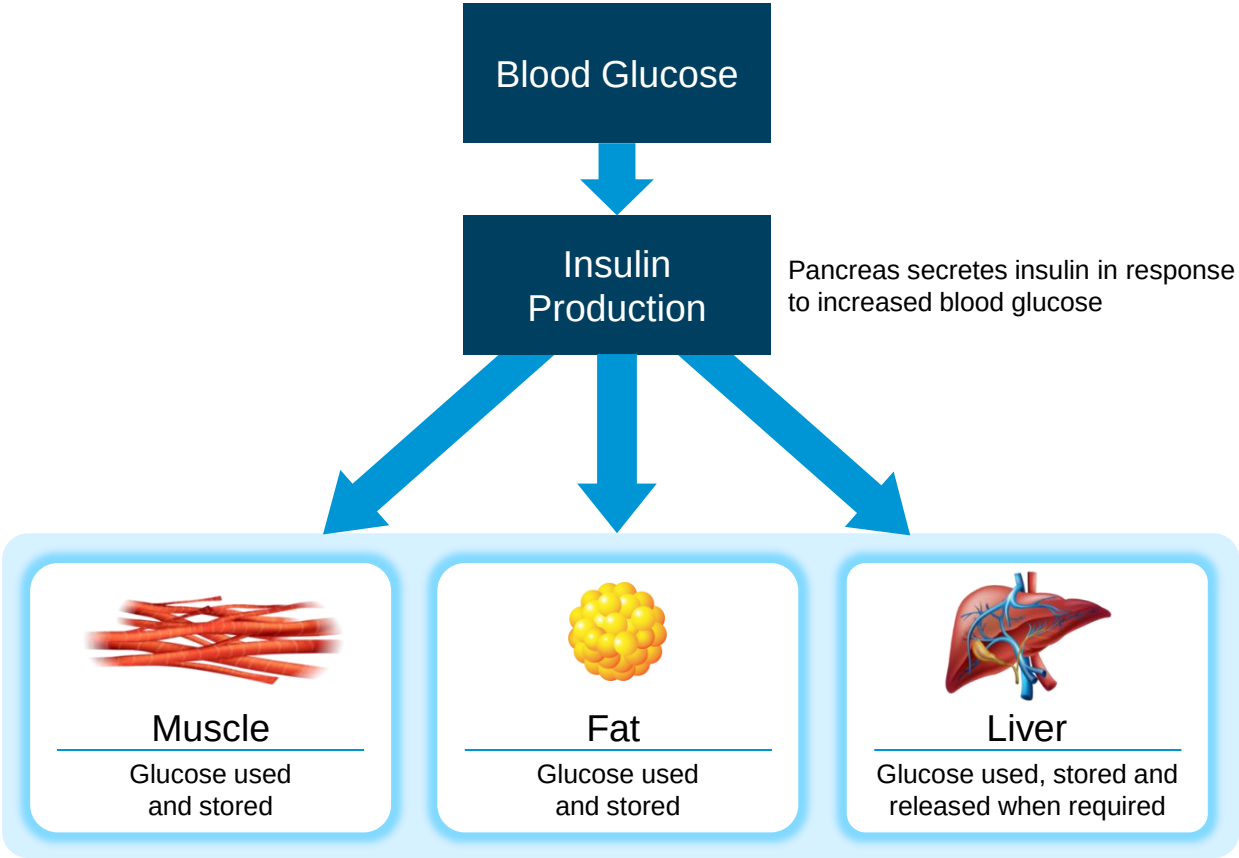
Glucose Clearance Involves Insulin and Peripheral Organs: Olanzapine Disrupts Normal Process



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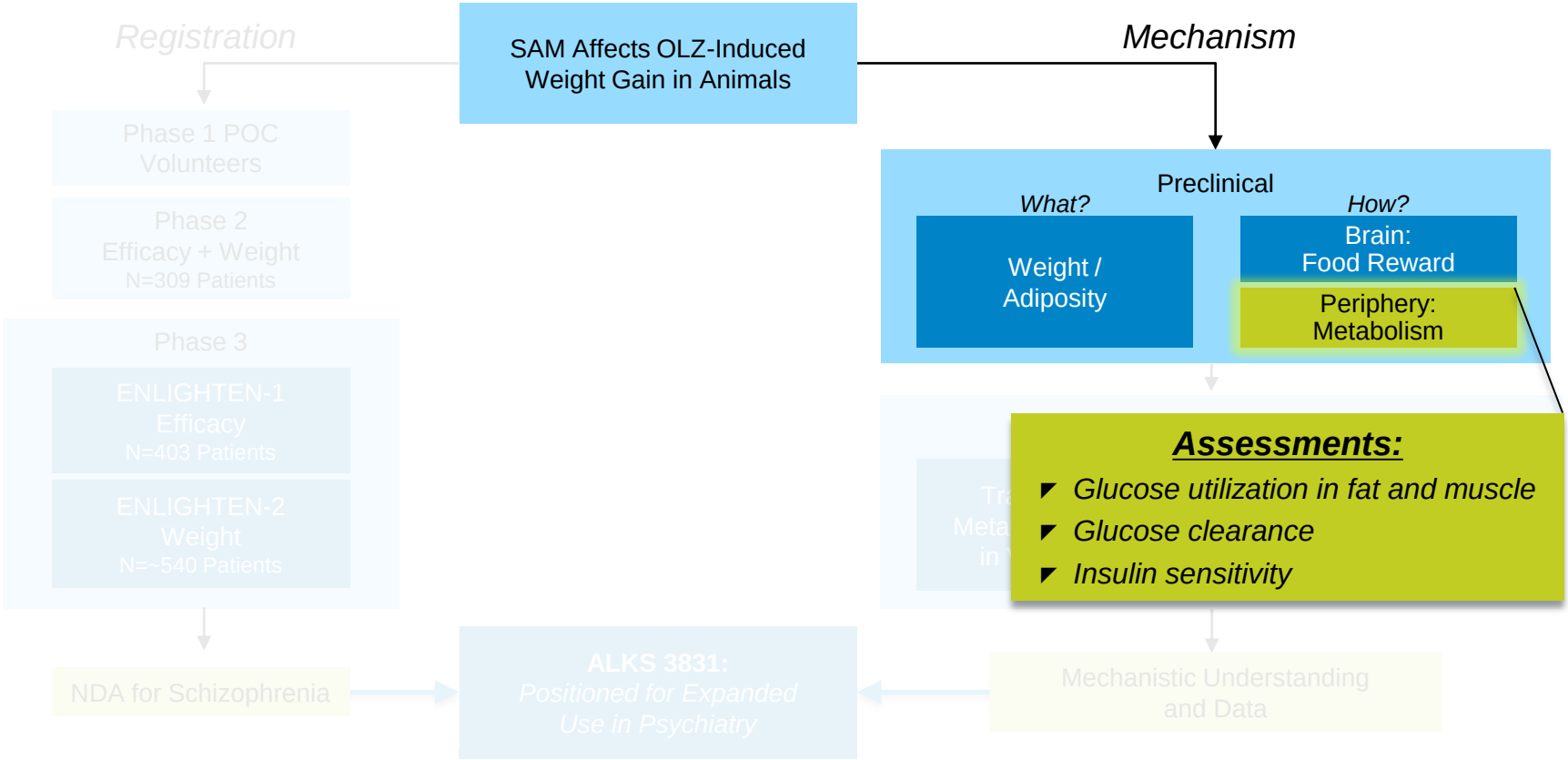
ALKS 3831 Development Pathway



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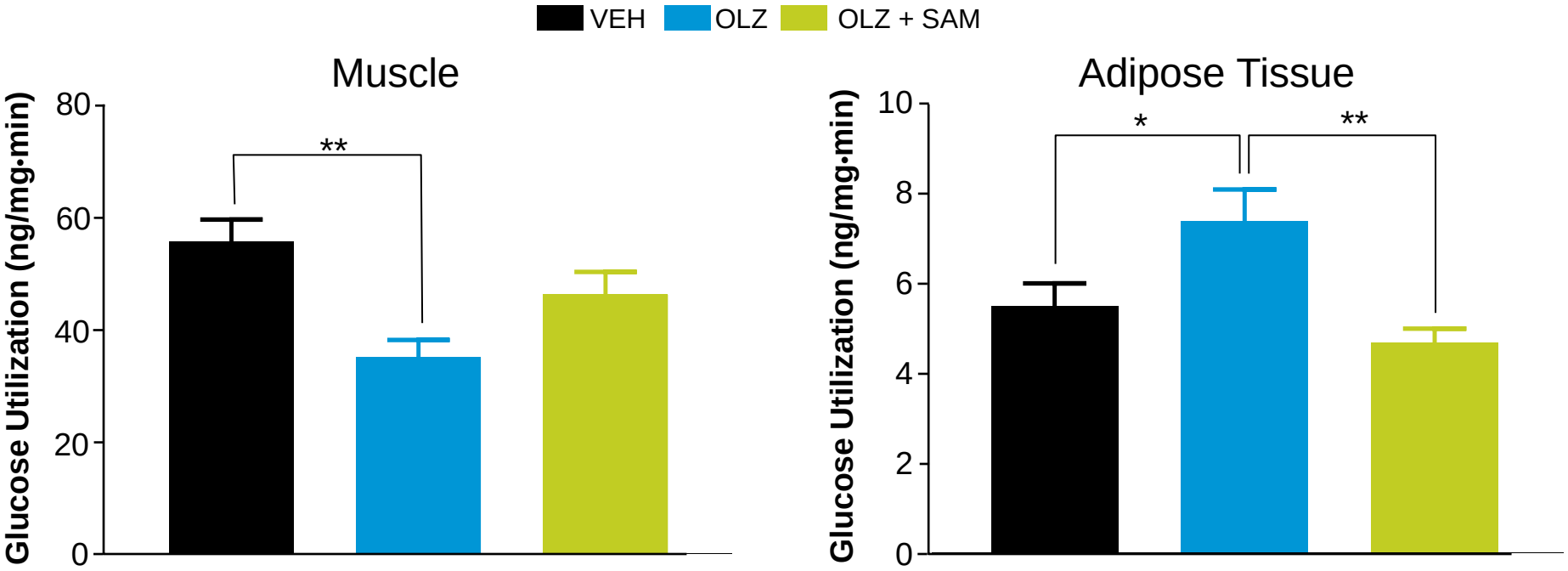
Samidorphan Attenuates Olanzapine-Induced Disturbances in Glucose Utilization in Muscle and Fat in Female Rats



**VEH vs. OLZ, $p < 0.001$

*VEH vs. OLZ, $p < 0.05$
**OLZ vs. OLZ + SAM, $p < 0.001$

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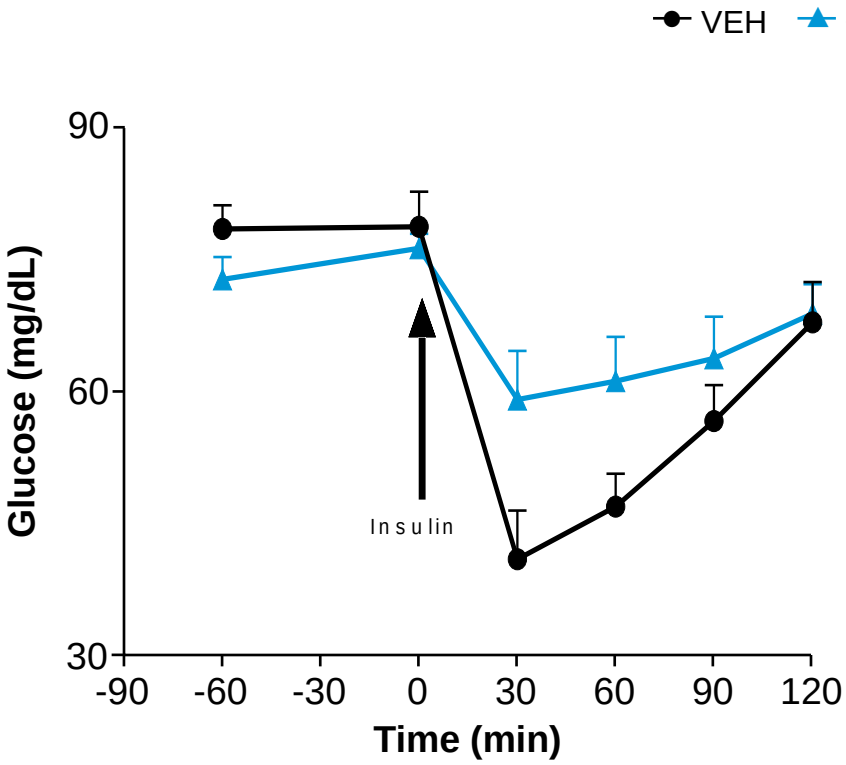
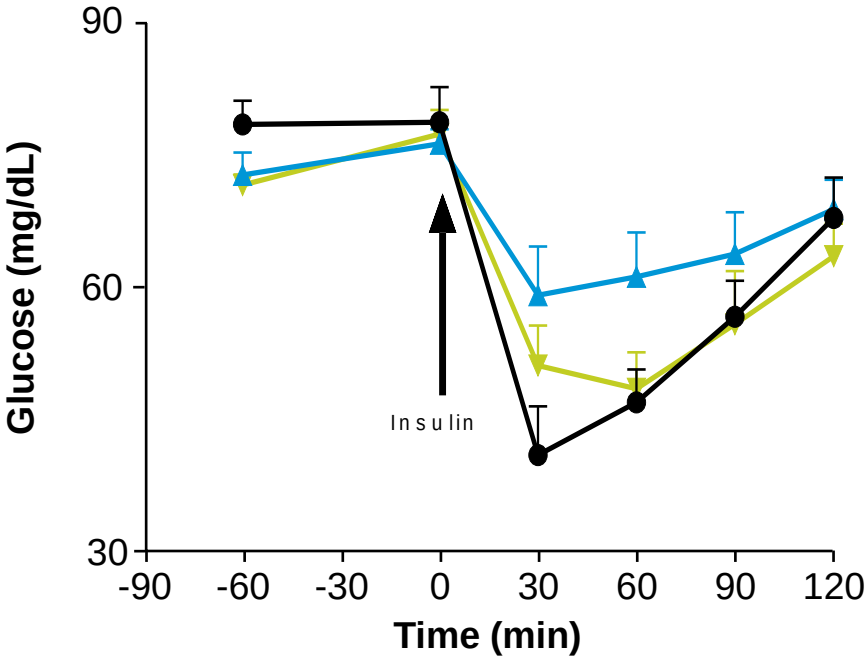
Samidorphan Normalizes Glucose Clearance in Female Rats When Bolus Insulin is Administered at Resting Glucose Levels



OLZ vs. VEH, $p < 0.05$



OLZ vs. VEH, $p < 0.05$

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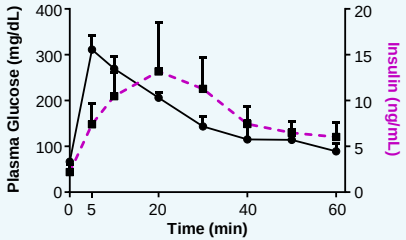
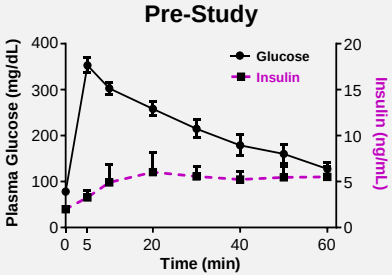
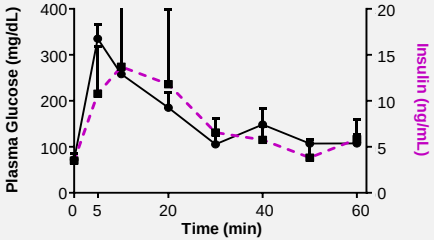
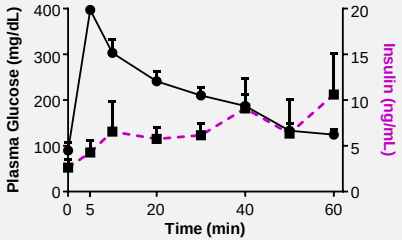
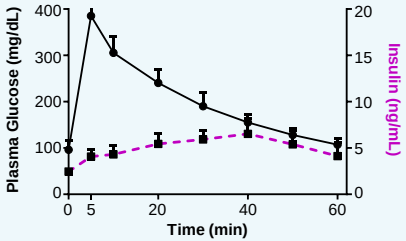
Samidorphan Prevents Hyperinsulinemia in NHPs Receiving High Fat Diet

Pre-Study Baseline		DAY 28	DAY 58
	VEH		
	**OLZ**		**Switched to OLZ + SAM at DAY 28** 
	OLZ+SAM		

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Summary of Preclinical Findings and Next Steps

Acute Effects		Chronic Effects	
Olanzapine	**ALKS 3831**	**Olanzapine**	**ALKS 3831**
Increases reward associated with food Alters glucose clearance – Decreases glucose utilization in muscle – Increases glucose utilization in fat – Decreases insulin sensitivity in liver	Normalizes reward associated with food Normalizes glucose clearance – Prevents and reverses hyperinsulinemia – Improves glucose clearance – Does not restore insulin sensitivity in liver	Increases weight Increases adiposity – Occurs with or without weight gain Progression to drug-induced metabolic syndrome	Attenuates olanzapine-induced weight gain Attenuates olanzapine-induced increase in adiposity Retains healthy metabolic profile

- Future research:
  - Interrogate how samidorphan normalizes glucose clearance and relationship to insulin sensitivity
  - Continue to characterize the effects of olanzapine and ALKS 3831 on caloric intake and energy expenditure
  - Investigate the effects of olanzapine and ALKS 3831 on circulating lipids
    - We have not observed consistent changes in lipid parameters in our preclinical studies to date

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Translational Phase 1 Metabolic Study

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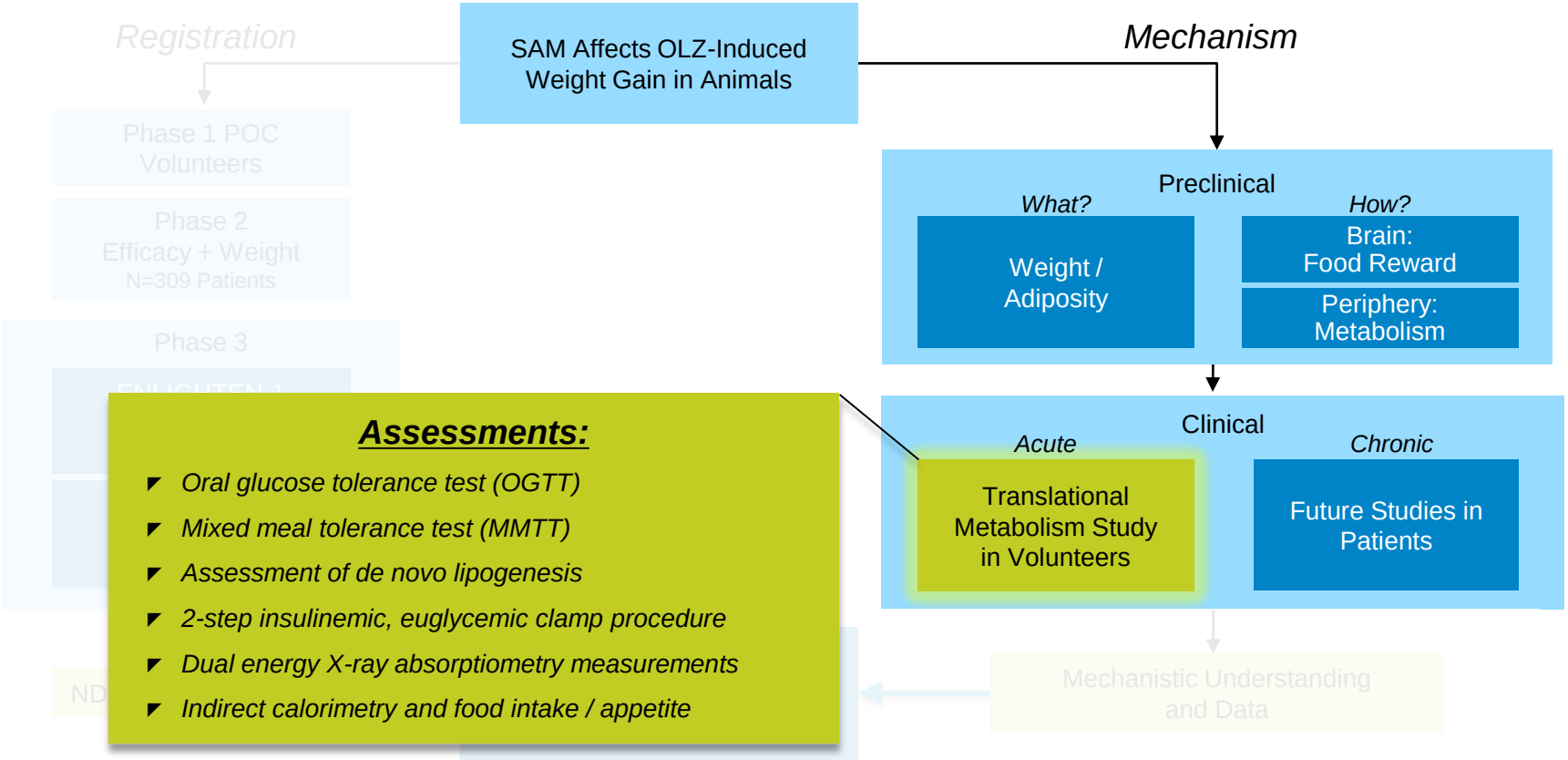
ALKS 3831 Development Pathway



Assessments:

- *Oral glucose tolerance test (OGTT)*
- *Mixed meal tolerance test (MMTT)*
- *Assessment of de novo lipogenesis*
- *2-step insulinemic, euglycemic clamp procedure*
- *Dual energy X-ray absorptiometry measurements*
- *Indirect calorimetry and food intake / appetite*

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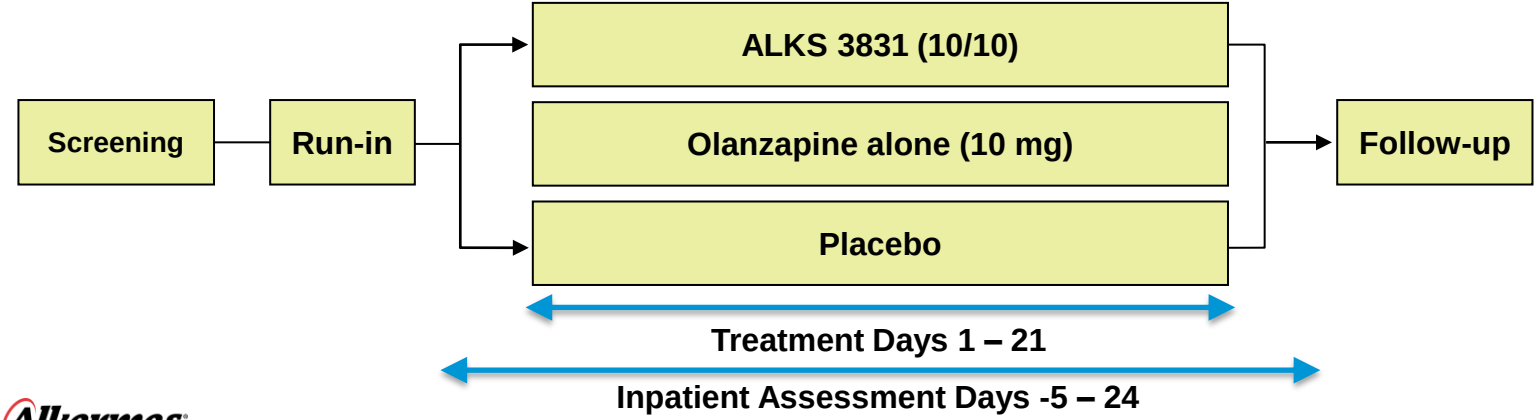
Translational Metabolic Study Details

- Goal: Gain insights into acute metabolic effects of olanzapine and ALKS 3831
  - Study designed to enable evaluation of acute metabolic effects that precede pronounced or prolonged weight gain
- Study design details
  - 60 healthy volunteers randomized 2:2:1 to ALKS 3831, olanzapine or placebo
    - Powered as an exploratory study (pre-specified threshold for significance p=0.10)
  - No regular exercise permitted from screening through end of treatment period



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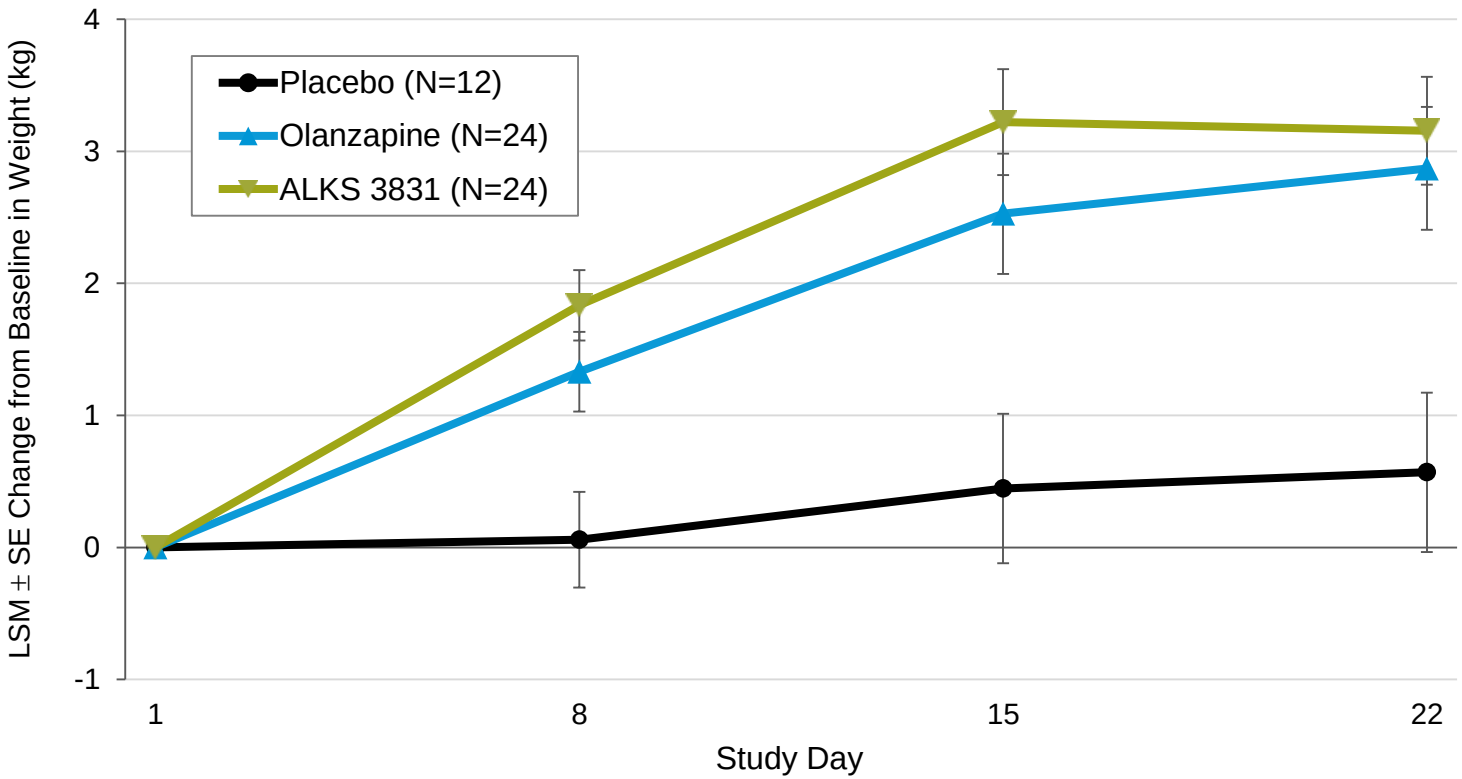
Weight Gain Profile of Olanzapine and ALKS 3831 During Initial Three Weeks of Treatment



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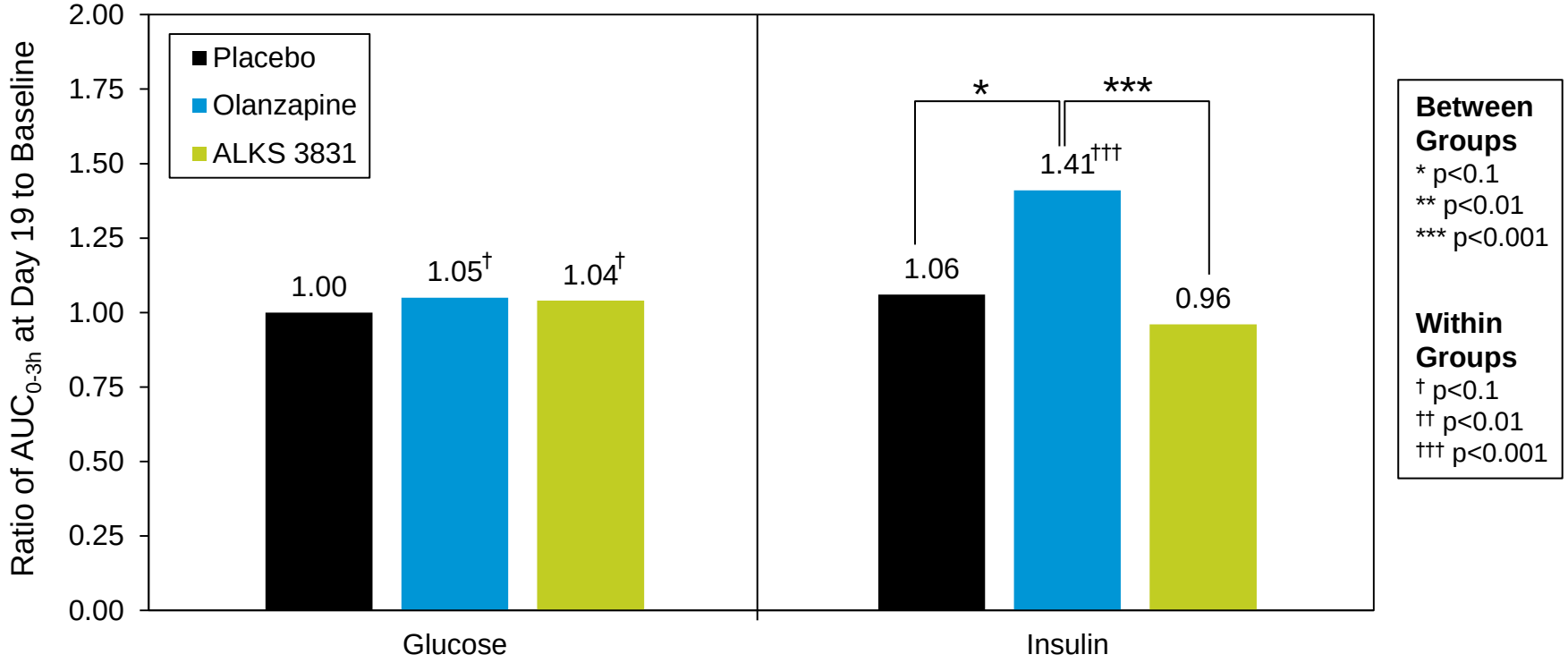
Oral Glucose Tolerance Test (OGTT): Olanzapine-Induced Hyperinsulinemia Mitigated by Samidorphan



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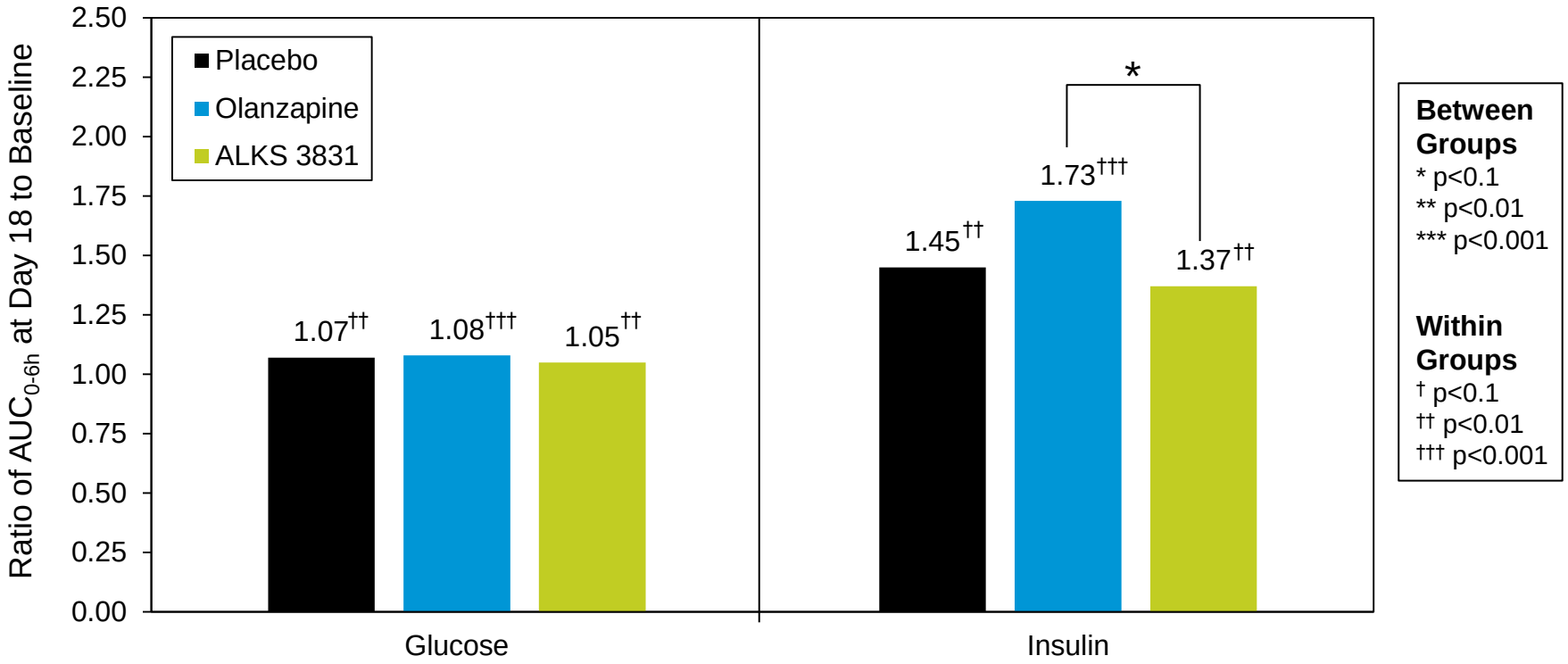
Mixed Meal Tolerance Test (MMTT): Replication of Olanzapine-Induced Hyperinsulinemia and Mitigation by Samidorphan



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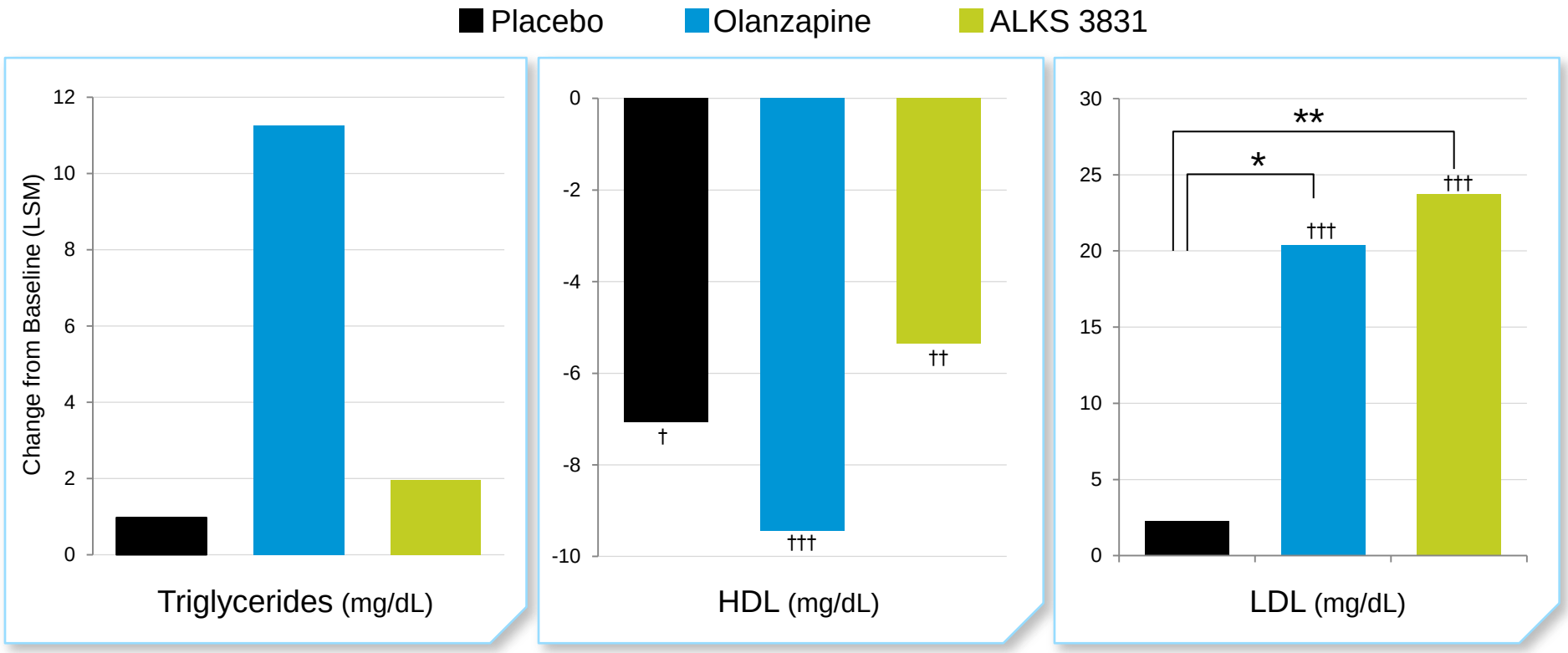
Acute Lipid Panel: Triglycerides, HDL and LDL



Between Groups	Within Groups
* p<0.1, ** p<0.01, *** p<0.001	† p<0.1, †† p<0.01, ††† p<0.001

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Learnings from Metabolic Study

- Samidorphan was found to mitigate olanzapine-induced hyperinsulinemia as assessed by OGTT & MMTT
  - Normalization of glucose clearance observed despite undetectable change in insulin sensitivity using a hyperinsulinemic euglycemic clamp
  - Recapitulated what was seen preclinically
- Lipid panels uninformative due to duration and nature of acute study
- Informative for future streams of research and optimal study designs

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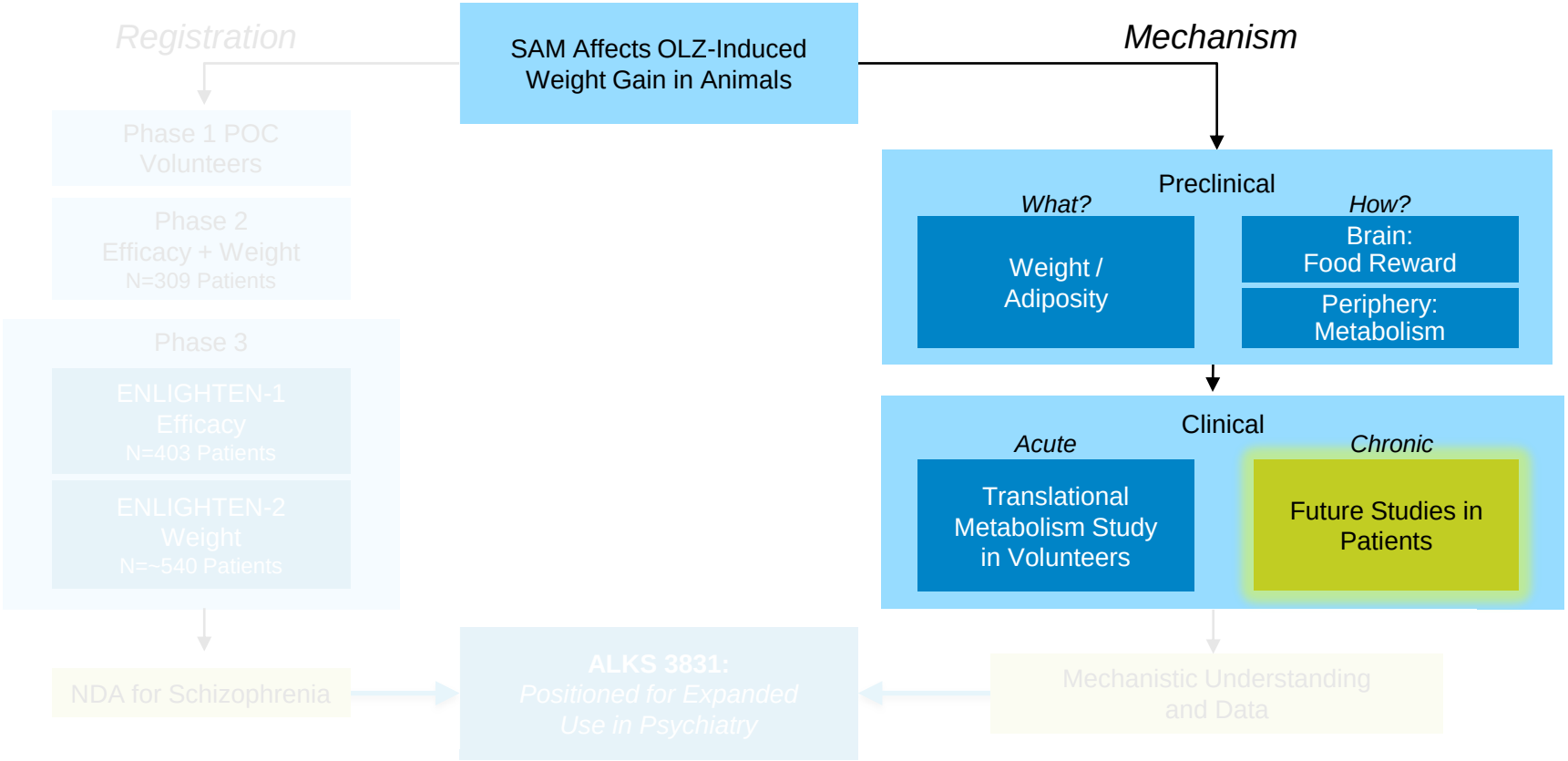
ALKS 3831 Development Pathway



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Weight
N=~540 Patients

NDA for Schizophrenia

Mechanism

Preclinical

What?

Weight / Adiposity

How?

Brain:
Food Reward

Periphery:
Metabolism

Clinical

Acute

Translational Metabolism Study in Volunteers

Chronic

Future Studies in Patients

Mechanistic Understanding and Data

ALKS 3831:
Positioned for Expanded Use in Psychiatry

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ALKS 3831 Development Pathway

Registration

SAM Affects OLZ-Induced Weight Gain in Animals

Mechanism

Phase 1 POC Volunteers

Phase 2
Efficacy + Weight
N=309 Patients

Phase 3

ENLIGHTEN-1
Efficacy
N=403 Patients

ENLIGHTEN-2
Weight
N=~540 Patients

NDA for Schizophrenia

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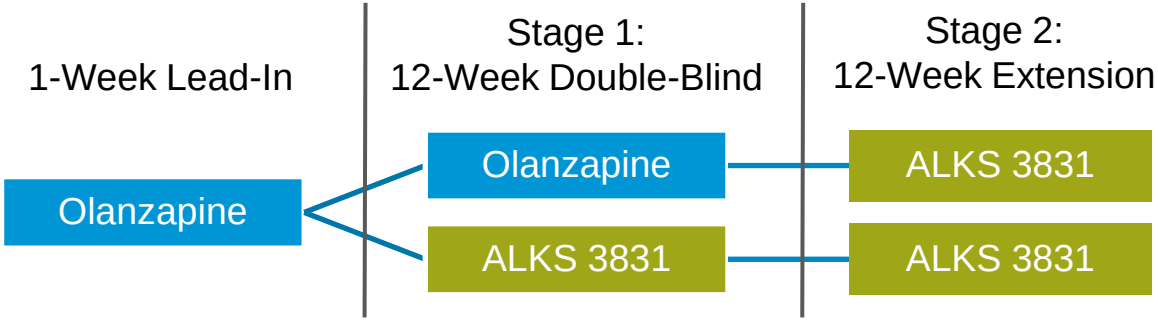
ALKS 3831 Phase 2 Study Assessed Efficacy and Attenuation of Olanzapine-Induced Weight Gain

- 309-patient, multicenter, double-blind, active-controlled, dose-ranging study
  - Following one-week oral olanzapine lead in, all patients randomized to olanzapine or three different doses of ALKS 3831 for 12 weeks (Stage 1)
    - Olanzapine + 5 mg, 10 mg or 20 mg samidorphan
    - Followed by 12-week extension period in which all patients received ALKS 3831 (Stage 2)
- Primary endpoint: PANSS total score at Week 12, compared to olanzapine
- Secondary endpoints focused on impact of ALKS 3831 on weight gain, compared to olanzapine



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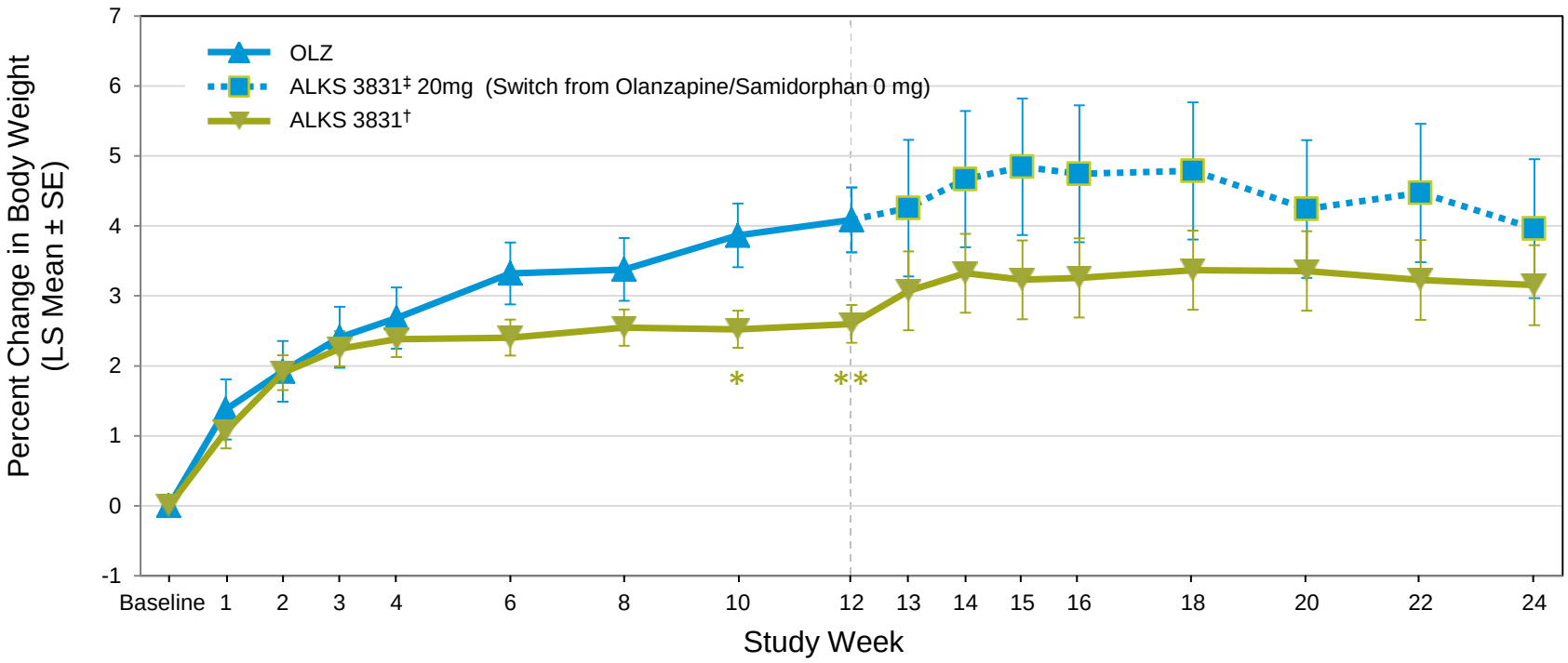
ALKS 3831 Phase 2 Study: Effect on Weight Gain



†ALKS 3831 combined treatment groups
‡ Switched to flex olanzapine dose plus samidorphan 20 mg

Note: Analysis based on MMRM
*p<0.05 vs. olanzapine; **p<0.01 vs. olanzapine

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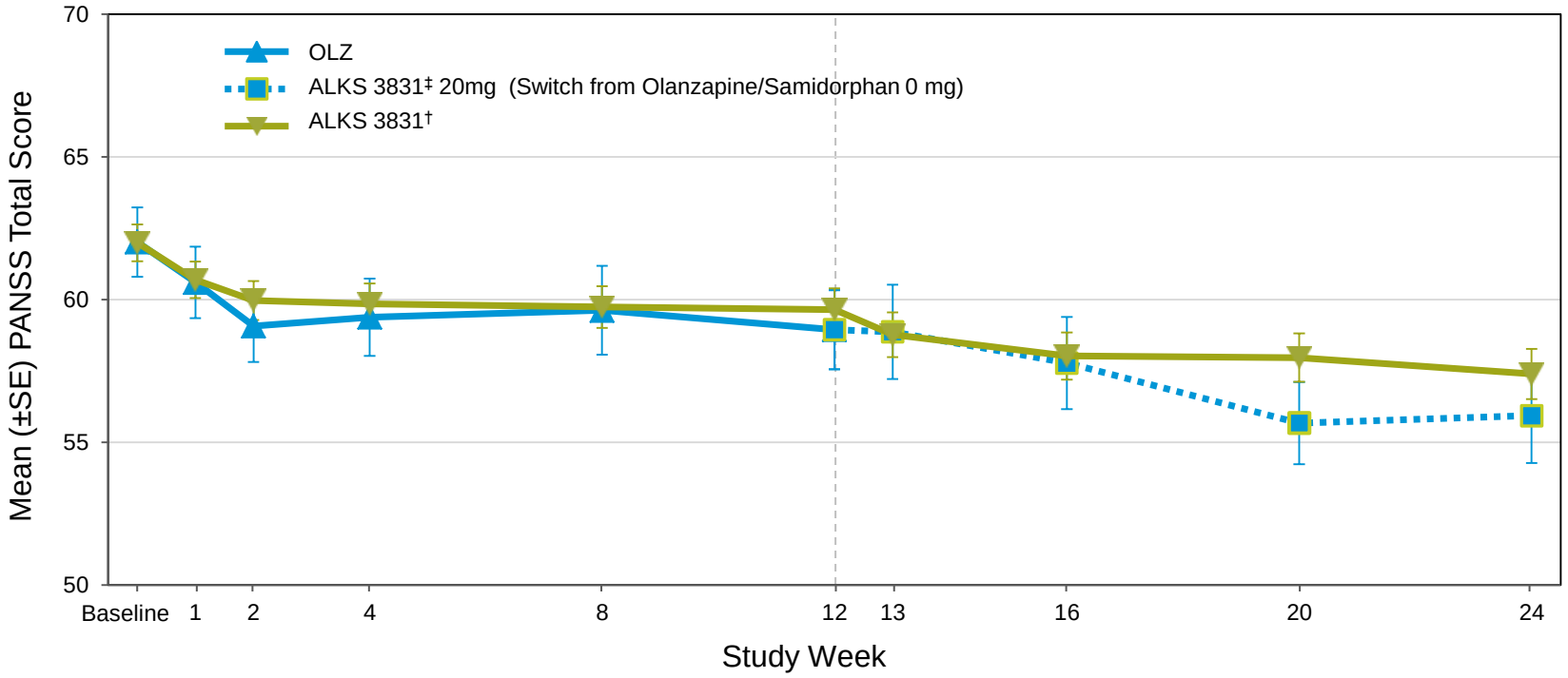
ALKS 3831 Phase 2 Study: Antipsychotic Efficacy



†ALKS 3831 combined treatment groups
‡Switched to flex olanzapine dose plus samidorphan 20 mg

Note: Analysis based on summary statistics

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ALKS 3831 Phase 2 Study: Safety Summary

- Safety profile:
  - AEs with a difference >5% vs. olanzapine: somnolence, sedation and dizziness; mild and transient
  - Low rates of discontinuation related to AEs (5% olanzapine vs. 8% ALKS 3831)
  - Low rate of serious adverse events (3% olanzapine group vs. 5% ALKS 3831)
- No significant trends or changes in laboratory values, vital signs or ECG
- Safety profile was consistent in both Stage 1 and Stage 2

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ALKS 3831: Straightforward Phase 3 Program Completing in 2018

ENLIGHTEN-1
Four-Week Efficacy Study

- Antipsychotic efficacy vs. placebo
- 403 patients with acute schizophrenia
- ALKS 3831 demonstrated statistically significant reductions from baseline in PANSS scores, compared to placebo ($p<0.001$)
- Olanzapine achieved similar improvements from baseline PANSS scores, compared to placebo ($p=0.004$)

ENLIGHTEN-2
Six-Month Weight Study

- Weight change vs. olanzapine in ~540 patients with stable schizophrenia
- Co-primary endpoints
  - Percent change from baseline in body weight
  - Proportion of subjects with ≥ 10% weight gain
- Data expected Q4 2018

NDA submission planned in H1 2019

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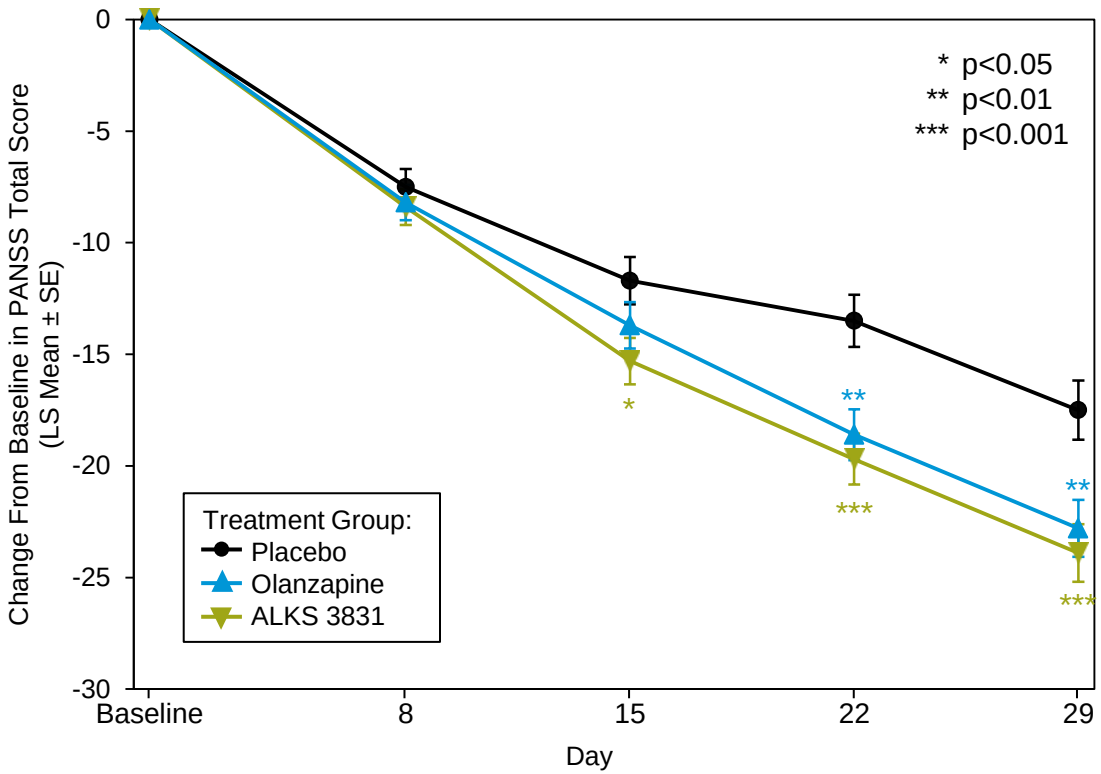
ENLIGHTEN-1: ALKS 3831 Phase 3 Antipsychotic Efficacy Study
Change from Baseline in PANSS Total Score (Primary)



Change from Baseline at Week 4	PBO (N=112)	ALKS 3831 (N=124)	OLZ (N=120)
Mean (SD)	-19.4 (14.80)	-23.7 (12.61)	-22.4 (13.63)
LS Mean (SE)	-17.5 (1.32)	-23.9 (1.28)	-22.8 (1.29)
LS Mean Difference (SE) vs. Placebo		**-6.4 (1.83)**	**-5.3 (1.84)**
P-Value		**<0.001**	**0.004**

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ENLIGHTEN-1 Phase 3 Antipsychotic Efficacy Study: Most Common Adverse Events

Treatment Emergent Adverse Events Reported with a Frequency of 5% or Greater and at Least Twice That of Placebo

	ALKS 3831 (n = 134) n (%)	OLZ (n = 133) n (%)	PBO (n = 134) n (%)
Any TEAE ≥5%	73 (54.5)	73 (54.9)	60 (44.8)
Weight increased	25 (18.7)	19 (14.3)	4 (3.0)
Somnolence	12 (9.0)	13 (9.8)	3 (2.2)
Dry mouth	10 (7.5)	7 (5.3)	1 (0.7)
Headache	8 (6.0)	7 (5.3)	4 (3.0)
Weight, kg, mean (SD)			
Baseline weight	77.9 (15.4)	82.2 (19.3)	76.6 (15.9)
Change in weight at Week 4	3.0 (3.6)	2.4 (3.7)	0.2 (2.8)

- No significant trends or changes in laboratory values, vital signs or ECG

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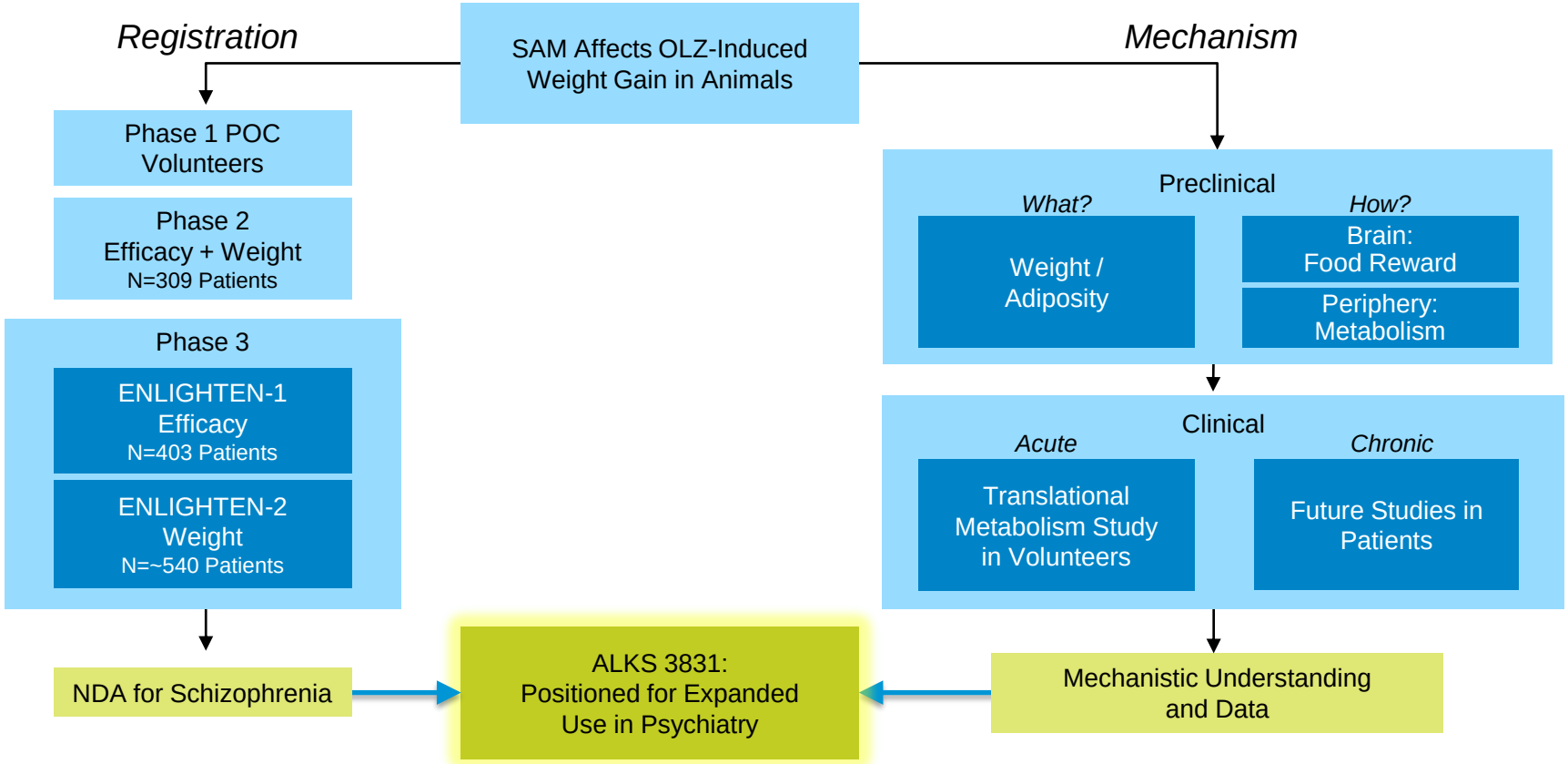
ALKS 3831 Development Pathway



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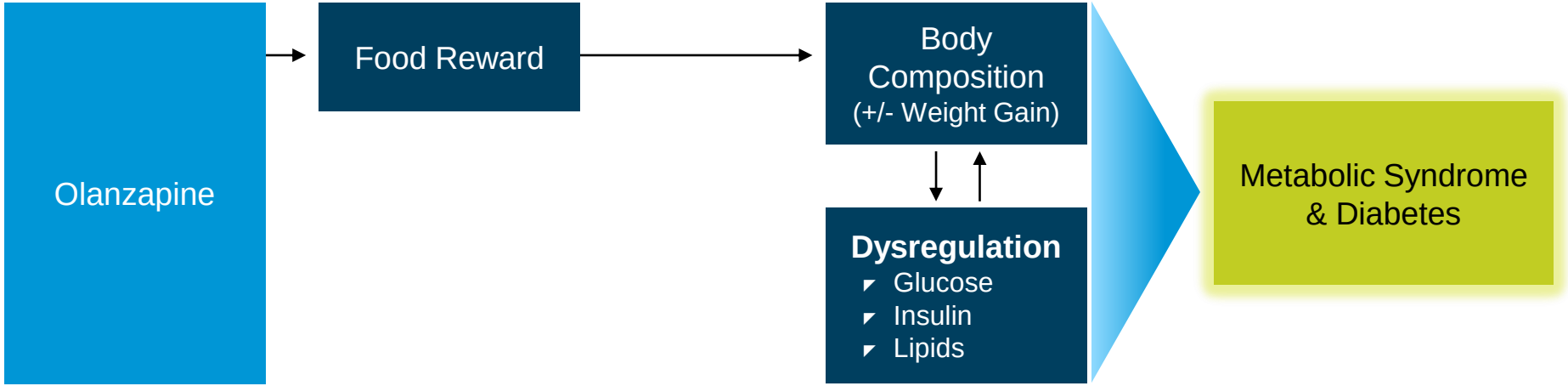
Original Hypothesis: Chronic Olanzapine Use Causes Multiple Metabolic Dysfunctions, Driven by Exaggerated Food Reward



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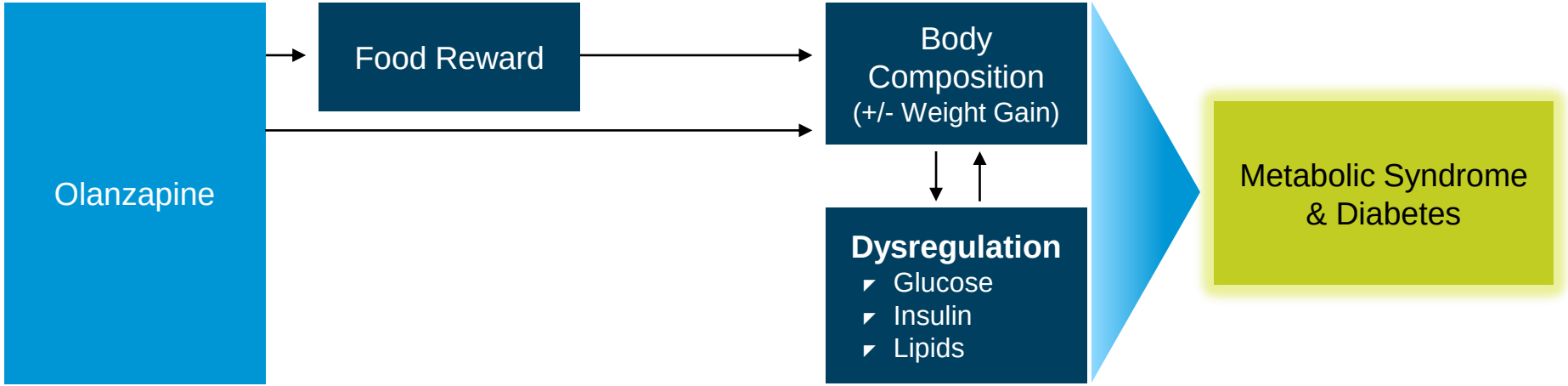
New Learnings: Chronic Olanzapine Use has Direct Effect on Body Composition, Independent of Food Reward Pathway



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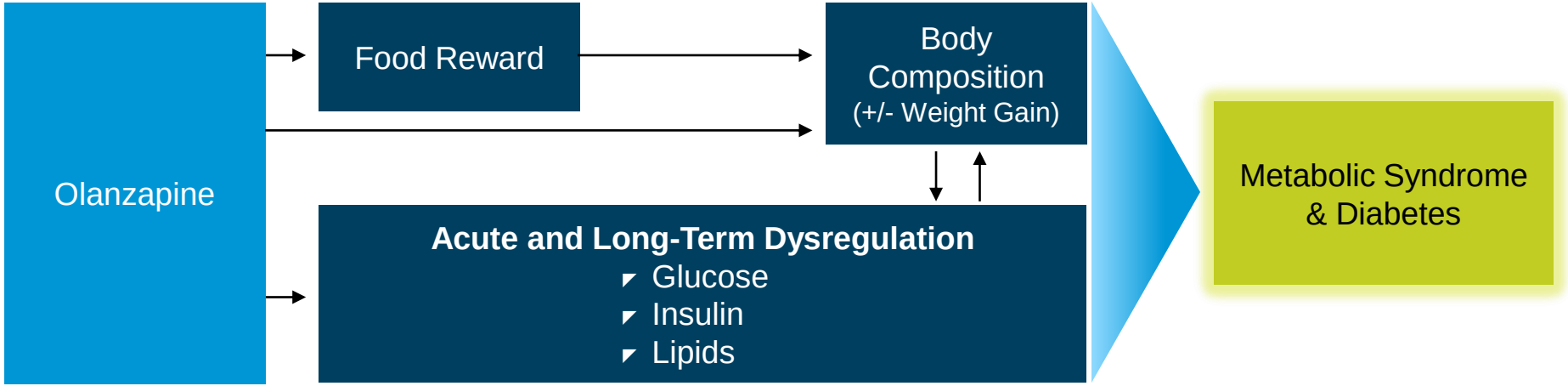
New Learnings: Olanzapine has Both Acute and Long-Term Effects on Dysregulation of Metabolic Functions



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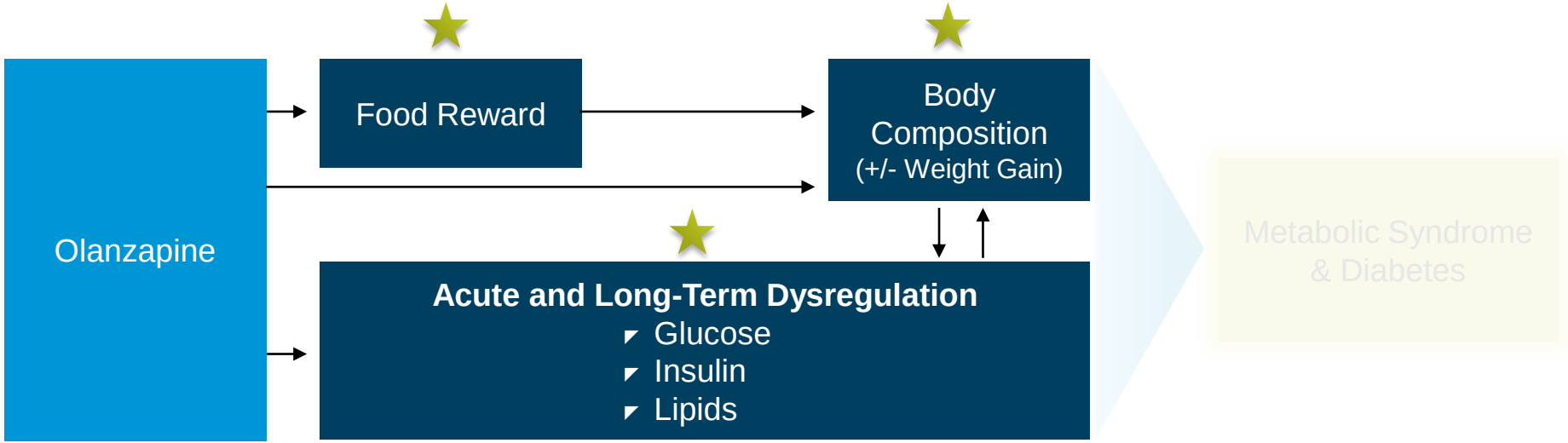
Samidorphan Disrupts Olanzapine's Acute and Long-Term Effects

★ Samidorphan



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Conclusions and Next Steps

- Samidorphan plays important multifaceted role in mitigating olanzapine-induced disturbances:
  1. Food reward
  2. Glucose clearance and/or hyperinsulinemia
  3. Weight and adiposity
- Additional mechanistic research planned to further interrogate long-term effects in patients
- Pivotal development program nearing completion
  - Antipsychotic efficacy proven in phase 3 ENLIGHTEN-1 study
  - Data from ENLIGHTEN-2 six-month weight study expected Q4’18
- Planned NDA filing H1 2019

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Q&A

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Craig Hopkinson, M.D., Chief Medical Officer, Senior Vice President of Medicines Development and Medical Affairs

Richard Pops, Chief Executive Officer

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